THE

PRINCIPLES AND METHODS

OF

THERAPEUTICS.

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TRANSLATED FROM THE FRENCH.

PHILADELPHIA, PA.
D. G. BRINTON, 115 SOUTH SEVENTH STREET.

1881.

Press of WM. F. FELL & Co.,
1220-1224 Sansom St.,
Philadelphia.

PREFATORY NOTE.

The work here laid before the medical public differs so widely from other treatises in the language on Therapeutics, that a few words as to its scope will not be out of place.

It is, as its title states, a discussion of the *principles* and the *methods* of therapeutics. It does not take up this branch as an accessory to Materia Medica; nor is it concerned, beyond a moderate extent, with the physiological action of drugs; nor yet has it much to say on the treatment of individual diseases. These topics, which figure so prominently in most works on therapeutics, will be found to occupy comparatively little space in the present one.

Professor Gubler chose to approach his subject from quite other directions and with other purposes. He aimed to represent, from the latest acquisitions of science, and by the aid of the most careful instructions, first, the *methods* which can be most effectively employed in the administration of remedial agents, and next the *principles* or *processes* by which their remedial action is exerted on the human economy. It is a study founded on clinical, physiological and chemical observations of the actions of medicines in disease, and the technical artifices for their introduction into the organism.

Approached with this understanding, his lectures will be found most fruitful to the careful student. They will explain many apparent contradictions and obscurities which often puzzle and sometimes dishearten the practitioner. It is true that his style is at times involved, and his reasoning not always easy to follow; but the labor to grasp his thought will certainly be found to be remunerative.

The translation has been made by Dr. M. J. Halloran, a former pupil of the author, and Mr. Charles A. Poizat. The biographical sketch has been furnished by the former.

The metric weights have usually been preserved in the text, as they are now familiar to American physicians. Their proximate values may, however, here be added:

1 milligramme,= - - - - - -	gr. $\frac{1}{60}$.
1 centigramme,= - - - - -	gr. $\frac{1}{6}$.
1 gramme,= - - - - - - -	gr. xvss.
1 kilogramme,= - - - - -	lbs. ijss.
1 centimetre,= - - - - -	$\frac{4}{10}$ of an inch.

BIOGRAPHICAL SKETCH

OF

PROFESSOR ADOLPHE GUBLER.

M. Gubler, Professor of Therapeutics of the Faculty of Medicine of Paris, was one of the most remarkable figures in the modern French school of medicine.

A worthy pupil of Trousseau, he was at once an able clinical teacher and a distinguished botanist and chemist. His works, his teachings, his lectures on therapeutics, admirable as regards the doctrines inculcated and for their scientific value, placed him in the foremost rank among contemporary scientists.

His real name was Goblet, and he was born at Metz, April 5th, 1821. His parents were in very moderate circumstances, and settled in a village near the Belgian frontier, where he attended school, and profited so well from his lessons that at the age of thirteen his masters had no more to teach him.

An attack of pleurisy, brought on by submersion in a frozen pond, retarded his studies for a considerable period. On his recovery he was placed with an uncle, a druggist, at Rocroy.

Here Gubler found, relegated to the topmost shelves of the library and covered with dust, various old books, which he examined with curiosity; they were ancient treatises on botany, and among them he became particularly interested in the venerable "*Traité de la Vertu des Plantes,*" by Guy de la Brosse, and the "*Historia Generalis Plantarum,*" by Delechamps.

A new life opened before him; his days were passed in the fields, and in the evening he attempted to compare the specimens collected with the descriptions of his books. Soon recognizing their imperfections, he mapped out and created for himself a system of botany which was admired by teachers of eminence. He even wrote a monograph on mosses, which he subsequently destroyed, but which merited preservation for the accuracy in description and the high standard of the general views expressed by a youth of fifteen.

In later years he recalled with grateful recollection the laborious yet happy period of his youth passed in the little village of Rocroy. A year later he was sent to school at Metz, where he terminated brilliantly his studies, and in

1841 set out for Paris, poor in money but rich in hope, and sustained by an indomitable will.

His success was marked and rapid. In 1844 he received the first prize at the Practical School, (dissections,) and in 1845 he was appointed interne in the Paris hospitals. It was at this period of his life that an accident, which nearly proved fatal, rendered his health, already delicate, still more precarious.

Baudelocque one day asked Trousseau to select for him a distinguished interne, to accompany on his travels a young man of good family, who was in a state of extreme mental distress, brought on by participation in a duel. Trousseau immediately thought of Gubler, who refused to leave his studies until Trousseau desired it as a personal favor, when he acceded. All went well until they arrived at Milan. By the change of scene the young patient had almost regained his usual spirits. At Milan, however, he again thought himself pursued by his enemies, and desired Gubler to occupy the same room with him. During the night he suffered very much from hallucinations, and Gubler was obliged to leave his bed to calm the patient. This he succeeded in doing, and was in the act of returning to his own bed, when he heard the click of a pistol; he turned towards his patient, and received a bullet full in the chest; he fell, and the maniac threw himself upon him, inflicting wounds of great gravity, with a knife, on the chest, neck and abdomen. Gubler was taken to the Milan hospital, where his recovery, at first very doubtful, was brought about, notwithstanding the penetrating wound of the chest and the development of peritonitis consecutive on the abdominal wounds. The cicatrices in the neck were of such extent that he was accustomed to wear his hair long to conceal them.

He thus lost a year from his studies, for his convalescence was slow. The ball was never extracted, and he attributed to its presence many of the troubles from which he suffered in later years.

In 1848 and 1849 his first memoirs, principally on botanical pathology; on the development of galls; on the tumors observed on apple trees; on the existence of a new form of fungous growth in diseased olives, were presented to the Society of Biology, then newly founded.

These were not isolated observations, without ultimate object; Gubler intended them to form part of a work on comparative pathology, which he always intended to produce; indeed, throughout his works are many evidences how much this subject occupied his attention, as in his papers on the discovery of a growth in the mucus contained in bronchial dilatations; observations on the diseases of fishes; the anomalies observed in a case of hermaphrodism and exaggeration of size (géantisme) in the pisticia lentiscus.

In his work on the origin and conditions favorable to the development of the oidium albicans, he showed that acidity of the saliva is a necessary condition for the development of thrush (muguet), and that when the cryptogamous growth is fully developed, it renders the saliva acid, and also acts as a special ferment, at least for saccharine matters. He demonstrated also that the trans-

mission of this growth is a true transplantation; that it is not a pathological product, but simply an epiphenomenon in the course of various affections which present in common digestive derangements, in conjunction with an abnormal condition of the buccal secretions.

In a second memoir, Gubler combats, with striking arguments, the idea of indefinite transformation (evolution) put forward by Lamarck and Darwin, and shows himself a partisan of the relative fixity of the various species of animal life.

These researches entered but casually into his projects. He desired especially to be known as a clinician, and he entered upon the study of clinical medicine with such ardor that within a year after receiving his degree he was appointed chief of clinics, and later, physician in the Paris hospitals, although it was his first concours.

Two years later, in a brilliant concours for the *agrégation*, he sustained his "Thesis on Cirrhosis," a work which has remained classic on the subject. In it he established the true theory of the malady; the genesis of intestinal hemorrhage in diseases of the liver; the history of the collateral circulation when the organ is profoundly affected and the distinction between the atrophic and hypertrophic forms of cirrhosis.

From this period Gubler commenced to realize the dreams of his youth. In 1852 he was elected Vice President of the Society of Biology; in 1862 and 1866 the Botanical Society did him the same honor; in 1865 the Academy of Medicine elected him one of its members, and during the same year he was made chevalier of the Legion d'Honneur, for his services at the Beaujon Hospital during an epidemic of cholera.

Finally, in 1868, he received the supreme reward of a life of scientific labor —he was made Professor of Therapeutics in the Paris Faculty of Medicine.

Chemistry, pharmacy, natural history physiology, pathology, anatomy, all sciences in which he was deeply learned, served to render his lectures extremely interesting and brilliant, and aided much in the new impetus given by him to the science of therapeutics.

Later, when the Academy of Sciences decreed to him the Chaussier prize for his great work, "*Commentaires Therapeutiques sur le Codex*," his friends urged him as candidate for the Institute, and twice in succession the section of medicine and surgery of this learned body presented him at the head of their list of candidates.

The list of M. Gubler's works is very extensive, and many of them have taken rank in science as definitive discoveries: as his inaugural thesis on the functions and pathology of Mery's glands; his memoirs on the existence of muciparous glands in the gall-bladder, demonstrating the contractility of the veins; on the presence of sugar in the lymph, which he asserted contained also normally incomplete blood corpuscles—whence the doctrines at present received regarding the part played by the lymphatic system in blood formation.

He studied also the lacteal secretion observed in newly-born children, and

the physiology of sleep, founded on the existence of a static hyperemia of the brain.

In applied chemistry his labors have been of equal importance. He demonstrated the alkalinity of the urine during convalescence; the transitory glycosuria of the period of reaction in cholera; the passage and diagnosis of the biliary resins in true hepatic jaundice; finally, the discovery of the chemical properties and clinical signification of the presence of indican, or indigose, in the urine. He established also the possibility of distinguishing, by examination of the urine, between true inflammatory and malignant fevers; he demonstrated that, in certain dyscrasic states, albuminuria being present, the renal apparatus becomes secondarily involved, the symptoms taking thereafter the appearance of true renal disease.

All these constitute so many applications of chemistry to the study of the pathology and diagnosis of disease.

He was, in a word, one of the founders of the application of biological chemistry to the study of clinical medicine, both by his own works and by the direction he gave to the researches of his pupils.

His works on medicine and therapeutics are of still more importance.

He published researches on the hepatic lesions observed in the syphilis of the newly-born child; on the pathogenetic and clinical distinction between jaundice due to hepatic derangement and that due to a dyscrasic state of the blood; also an important work on the forms of paralysis consecutive to acute diseases; the discovery of the cause of incomplete hemiplegia, the face being affected on one side, the limbs on the other (cross hemiplegia, *paralysies alternes*)—an advance towards the doctrines of cerebral localization on which Charcot has shed such lustre; also memoirs on the distinction to be established between diphtheritic and herpetic sore throat: and on internal erysipelas, laying down the general law of the simultaneous development of the inflammation on the cutaneous and mucous surfaces.

After freeing therapeutics from dogmatic prejudices and empiricism, Gubler bringing into play his universal erudition, soon placed himself among the authorities on the subject. He brought into common use, through his recommendations, aconitia, bromide of potassium, Calabar bean, chloral, eucalyptus, bromhydrate of quinine, and particularly jaborandi.

After the Franco-German war, he took up the study of the mineral springs of Europe, and, although rendering justice to those beyond the Rhine, he demonstrated that none of them were superior to the waters of the Pyrenees, the arsenical waters of Manif and of Mont-Doré and others.

In his private character he was universally beloved. Many a needy student he aided by advice and pecuniary advance. He spent each year a large sum among his patients at Beaujon Hospital, and he made a donation for the permanent support of a bed.

He loved young people, encouraging their efforts and not seeking to repress the ardor of imagination. He received them with large hospitality at his

house, rendered more pleasant by the presence of his amiable wife, a daughter of the sculptor, David D'Angers.

Like his predecessor, Trousseau, he succumbed to a chronic affection of the stomach, but he continually put off the period of repose rendered necessary by his declining health.

Towards the close of 1878, he was president of the board convened for the Concours of Internes. The subject given was albuminuria. The writer was present at the earlier readings, and almost every candidate referred to the researches of Gubler. He must have felt flattered, for the subject to be treated at the Concours is drawn by lot and the candidates locked up, so they have nothing but the memory to draw upon. He must have then remarked the wide-spread influence of his teachings. But before the Concours was finished he was obliged to give up, and retired to his villa, near Toulon, where he expired April 20th, 1879, in his fifty-eighth year.

A few words from his own writings will best characterize his method: "For those who cultivate the science of man there are two principal methods of seeking the truth. While some, taking a side-path leading to rapid results, seek through experimentation on animals to establish the fundamental laws of vital organization, in order to make applications of them to the human species, others interrogate man himself to obtain the information he alone is capable of giving, and attempt, by patient and laborious observation, to distinguish among the phenomena common to man with all living beings those peculiarities of organization and function proper to him alone.

"The first are known as experimental physiologists; the latter are simply physicians.

"All contribute equally to the advancement of biological knowledge, each one in the measure of his own personal capacity; and absolute pre-eminence cannot be attributed to either of the methods into which is subdivided the great and essentially modern scientific method."

TABLE OF CONTENTS.

THE PRINCIPLES AND METHODS OF THERAPEUTICS.

CHAPTER I.

General Therapeutics.

GENERAL THERAPEUTICS: Therapeutics first commenced by empiricism Difference between a *remedy* and a *medicament.*

REMEDIES: *Moral*—Love, victory, music, reading, travels, amulets, homœopathy.

Ponderable—Mechanical apparatus, percussion.

Biological—Globules of the blood, virus, hybridity, ethnics.

MEDICAMENTS: Attempt at classification by naturalists, chemists, therapeutists and physiologists.—Dangers attending all classifications.

PHYSIOLOGICAL PROPERTIES: *Mechanical Action*—Mercury, oil of sweet almonds, mucilages, charcoal, tannin, ammonia, iodine, and bromide of potassium.

Chemical Action—Old theory, effect through presence, alcalinity, acescence.

Histological Combination—Its laws.

Dynamic Action—Applications of the theory of the correlation of forces.

GENTLEMEN:

During a long series of ages those who practiced the art of healing, handled remedies in about the same fashion as children use gunpowder—aware of the marvelous or terrible effects of their weapons, but having no idea as to the nature of the force brought into action, its real power, the exact course of the pro-

jectile, or its range. In other words, old-time physicians not having the necessary exact instruments for the rigorous evaluation of phenomena, and being deprived, moreover, of all means for experimental control, could but imperfectly realize the intensity of action of remedies and their operative mechanism; they were unacquainted with the means of introduction and dispersion of remedies, their organic relative affinities, the alterations they underwent through the system, and the paths followed by them in leaving it. In this first period of empiricism, therapeutics was indeed no more than the art of healing.

After a time therapeutics became a real science, having its own principles, its methods, and its processes of investigation—processes, method and principles which it holds in common with physiology, of which it is a dependency. Only since the knowledge we have obtained of organism and the modifications it can be made to bear, can we make certain useful distinctions.

In the first place, we can distinguish a *remedy* from a *medicament*. Remedies and medicaments are not to be confounded; the term *remedy* may be applied to everything that can be made use of in healing. You will in due time see that the agents that can be thus used are in great variety; on the other hand, medicaments are relatively limited.

There are all sorts of means of curing. We have at our disposal moral, physical and material means; among these there are those that are imponderable. Who among you is ignorant of the marvels of *electricity?* The other imponderable fluids are equally called upon to render real services to the art of healing.

From ponderable substances we often expect the most varied results: you will find that there are some whose coarsest physical properties are utilized, while from others we expect more intimate actions.

A few words upon each of these great divisions among remedies.

Let us first speak of the *psycho-moral* treatment. One must

know but little of life not to be aware of the influence which the moral has upon the physical. If Cabanis has been able to write a book upon the influence of the physical on the moral, a work of equal interest could be compiled on the influence which the moral has on the physical. As a legendary example we have Erasistrates guessing that Stratonica was in love with Antiochus Soter, and curing his patient by a marriage. Examples like these are not rare; you probably have met with them. They are not always within the domain of science. You have but to read what all army physicians have written on the part which moral influence bears on the consequences of wounds. Whenever an army is victorious, wounds heal; if it be defeated, they are aggravated. I have said enough to make you understand that influence.

It is, therefore, indispensable to use such means as are capable of rousing the moral forces. These means you will employ not only against diseases, so called, of the mind, but against all others as well. We make use of moral means not only in cases of mental alienation and in exhaustion, but in diseases of long standing, among those affected with tubercles, with cancers, and with disorders of the heart. At times we appeal directly to the mind in order to rouse it; this is not the best method, I confess; it is even an ineligible one, especially where deep disorders of the mind are concerned. To one talking out of reason, it would seem natural for us to present him with a well-constructed syllogism; but this method in such a case is hardly ever successful. Better success is met with by acting indirectly upon the imagination; as for example, when passion is appealed to through the medium of the senses. You all know the influence of music, and the results obtained from it. Reading, relaxation and especially changes of air and place, presented to those whose minds are slightly affected, all these supply excellent means of improvement.

In a word, there are innumerable circumstances in which you will be obliged to uphold the courage of patients suffering under long and almost always fatal diseases; in some cases you will

even have to deceive them. It is under such conditions that certain means now out of use—and which I do not recommend—various superstitious practices in archaic medicine have been of use; for example, amulets and incantations.

At the present day we have them in infinitesimal doses; homœopathy is nothing else. You smile? I am able to tell you of a recent instance. Not long ago Dr. Potain and myself were called upon to attend a patient who thought himself suffering from a disease but of a few days' standing. He was under the care of a celebrated homœopathist, who kept up his courage and dosed him with cold water. Up to that time the patient experienced nothing more than slight fatigue; he was a great huntsman, but could no longer enjoy his pastime as was his wont; all at once formidable symptoms develop; he is taken with vomiting of blood. The homœopathist becomes frightened; he did not believe the disease was so serious, but now concludes to call in physicians. That unfortunate patient had an organic disease of the heart which had not been detected.

In conclusion, I may add that our pseudo-brother asked leave to return for the purpose of upholding the patient's courage. This, evidently, was the object he had in view; there is nothing culpable about it, but a similar result may be obtained by other methods. I repeat it, it is proper to encourage a patient, to indulge him even with well-meaning falsehoods, for there never was a case to which some relief could not be brought, and that is what is expected of you; the patient must have his illusions sustained, consoling words are to be spoken to him, according to the precept of Pindarus, who in his Pythics advises us "to charm suffering by kind and consoling words."

The therapeutic agents supplied by imponderable forces are interesting. It is not customary to dedicate a chapter to thermotherapeutics, yet valuable considerations might be pointed out in it.

You all know the influence of heat in the recovery of strength and you are aware of the influence which light possesses.

We are especially indebted to ponderable substances for the

greatest services. They supply the arsenal of therapeutics, but they are used for different objects.

At times we look to them for their coarsest physical properties, as in external therapeutics.

It is here we place hydro-therapeutics both hot and cold, for douches do not only operate by heat and cold, and the re-actions which follow; they also exert a mechanical action, percussion.

But oftener ponderable substances are looked to for intimate molecular operations which take place in the very structure of our tissues, operations upon which we shall have more to say hereafter. These are the real pharmaceutical methods, the real medicaments; consequently they are the methods in the art of healing upon which I shall dwell.

Finally recourse is sometimes had to ponderable substances which not only possess the properties of matter, but are moreover endowed with those of organized beings, real *organisms*.

When I say that the vital properties of a certain number of bodies are made use of, I have reference to the blood globules. Introducing blood into an anæmic person cannot be called giving him a medicament.

The same may be said when we introduce a virus which has no typical form, but which nevertheless possesses a certain number of properties belonging to organized living bodies, and which behaves like a collection of organisms properly so-called. Vaccine virus is a remedy but not a medicament.

An interesting chapter in therapeutics is that which aims not at individuals, but at races. It contains the modifications we produce in organisms, by means of a cross established between individuals of the same species, endowed with opposite diathetic qualities and temperaments; or else between different species (I give to *species* the meaning of *species*, *ειδος*. I admit a single human genus, but different species, formed by more or less deep modifications, acquired in course of time by subjects which have lived under special conditions.) Well, I say that by crossings, we can advantageously modify morbid dispositions. For example, if it were true that the

negro race is exempt from carcinoma, would there not be an advantage, (I do not speak for the white race; it is always unpleasant to tint one's self,) but for the Hindoos to cross themselves with those superb races met with in certain parts of Africa, and thus place themselves beyond the reach of cancer? In short, whatever that idea may be worth, I assure you that in the crossing of lymphatic and bilious subjects, there are developed conditions for the disappearance of a certain number of diathetic diseases which are a plague upon some populations. I believe, for example, that if the Russians, with whom scrofula is so prevalent that they readily tell you, "Doctor, in my family we are all scrofulous," were to cross themselves with the Spaniards, the consequence would be a decrease of scrofula.

There are, therefore, a great number of remedies which are not medicaments. Medicaments, although forming but a fractional part of remedies, are nevertheless the most important portion of our therapeutic arsenal. They are innumerable, hence difficult to classify.

Many classifications have been attempted, resting upon different bases; at one time attention was given to the organoleptic properties; this was clearly a primitive classification; again an attempt was made to classify according to natural orders. Naturalists and botanists have favored this idea, which may be useful, since Linnæus has taught us a great truth by showing that substances which approach one another in their natural characteristics are in general very analogous, not to say similar as to their properties. But exceptions to this rule are so numerous that his classification could not stand against them. A classification according to chemical composition was also attempted; this proved to be no better, because enormous disparities exist between substances which resemble one another in their physiological action. Finally classifications have been made based upon therapeutic effects. We have all been tempted to make our own. For my part I have never had the pretension of making a therapeutic classification, but I have attempted one based upon physiological effects.

I hasten to admit that it is not any better than the others, and I add that an irreproachable natural classifiation, that is, one not fettered by system, is absolutely impossible. Without indulging in many details, I will explain the reason why.

The same substance, according to the constitution of the subject, according to conditions peculiar to the substance itself, may produce not only entirely different, but inverse effects. You may then understand how difficult it is to base our views upon the properties of a substance in order to classify it under any one head within the limits we may wish to establish, since other reasons may entitle it to an entirely opposite place.

I have now reached a very important question, and one that should be settled at the beginning of all explanations of therapeutics, considered in a general way. That question is the *mode of action* of the various substances employed as medicaments, and the different effects which these substances are called upon to produce.

In a number of works attempts have already been made to understand this intimate mechanism; but never in an abstract way has the inquiry been made as to the effects produced by medicaments upon living beings. We have to consider three kinds of actions—these are: *mechanical* and *chemical* actions, and those connected with molecular physics, which I ask your permission to call by the name of *dynamic*.

Mechanical Actions.—It seems at first strange that such actions should be attributed to medicaments. You will see, however, that a certain number of examples present themselves.

For instance, pure metallic mercury has been introduced into the intestine to resolve a volvulus: it acts by its weight in unfolding the intestine.

Oil of sweet almonds given as a laxative, is simply a method of facilitating the passage of the excrements through the intestines; it does not act as a substance capable of inducing a secretion.

For a similar purpose are certain mucilaginous substances taken as a drink. Thus you will find, especially in popular

practice, many persons who drench themselves with a more or less viscous solution, obtained by boiling flaxseed. This is a good way to facilitate the exoneration of the intestine.

Here are other facts: A peripheric excitation may be obtained by purely mechanical means. (I will not mention those that are simply remedies.)

At times it may be substances provided with very sharp-pointed and stiff hairs, which, penetrating through the epidermis to the dermis, produce an itching sensation by mechanical excitement, and consequently all the pheuomena of cutaneous irritation or awakening of sensibility, as well as those of revulsion, as it is obtained by energetic methods.

I shall say nothing about nettles, of which my teacher, Trousseau, and myself have made such frequent use, for the hair in nettles is imbedded in a gland which contains chemical substances that cannot be included in the study of mechanical actions

Powdered charcoal administered in quite a number of dyspeptic conditions, especially as an absorbent of gases, only acts as a mechanical agent, and yet it has been observed that this charcoal powder produces very remarkable exonerating effects. Other substances facilitate or impede the flow of liquids in the capillary tubes. Thus tannin reduces the facility with which blood circulates through the capillaries.

There are other substances which act in an inverse manner.

Ammonia, which, when in solution in water, facilitates its introduction in the capillary tubes, acts in the same manner in the capillary vessels of living individuals. Similar effects are produced by bromide and iodide of potassium which, in this respect, are absolute congenerates.

There are, therefore, a certain number of instances in which medicaments produce real physical effects. But a medicament generally operates through its *chemical actions*.

Formerly, effects from mere presence would have been admitted, but at this day, especially considering what we know of the laws of correlation of forces, such explanations can no

longer be allowed. Indeed, in order that a body should act, not only must it be present, it must be all the while yielding either force or substance. In the edition of 1846 of Trousseau's work, I myself held out the opinion that cyanhydric acid must act in the blood towards the globules by simply the fact of its presence; we now know that it acts by a perfect combination of hæmoglobine, arresting its functions. I repeat it: action through presence alone, no longer exists; medicaments act by forming combinations; these combinations are in great variety, and take place either with mineral organic substances, or even with the plasma or albuminoid principles of the blood, or finally, but at a later period, with the histological elements themselves.

In this purely chemical manner of acting of substances, quite different categories are to be established.

Carbonate of soda, or Vichy water, is introduced in the stomach for the purpose of neutralizing the acids which have formed there at the expense of the alimentary substances. That is the simple phenomenon as far as the action of the medicament is concerned, when the latter is considered as a chemical body; but by the introduction of alkaline substances, there is produced an increase of causticity in a certain number of the fluids in the general economy, first of all in the blood. On the other hand, when it is desirable to increase the acid qualities of certain liquids, such, for instance, as sweat and urine, acids are introduced. Although more difficult to maintain, this condition is reached in a certain number of cases.

In other cases, to which I but just now alluded, substances introduced into the circulation must combine with the plasma of the blood, and then take part in the formation of the histological elements.

Just here two cases present themselves: At times there are normal substances in the organism, which become real elements of it: for example, the phosphates and carbonates of the earths, iron, cod-liver oil. Other substances behave in about the same way, in so far that, after having entered, they combine with the plasma, and take part in the formation of the tissues; but then

these substances either exaggerate the proportions of normal substances, or, if they are closely similar to the substances, they substitute themselves for them. Here are a few examples:

You introduce a large quantity of sulphur into the economy; it belongs to the same natural group as oxygen, and, as such, will substitute itself for oxygen in the composition of the histological elements, and particularly in the nervous system.

But we are here in presence of a normal substance, since sulphur exists in the economy. Let us take a substance which does not occur in the organism: arsenic, for example. Well, it will behave like sulphur. It will substitute itself for a certain proportion of phosphorus, for the reason that arsenic and phosphorus are substances belonging to the same group.

All this is not simply a vision of the mind. There are facts which, to me, seem to demonstrate the truth of this method of acting among a certain number of substances. Fifteen years ago, I attended a woman who had poisoned herself with arsenic. She had taken, so she said, a large teaspoonful of arsenious acid. Just think what a terrible quantity of poison that represents. After the choleriform accidents, she experienced febrile phenomena, and presented, finally, a paralytic state so very similar to saturnine paralysis, that Duchenne (of Boulogne) was deceived by it. But this is not, for the time being, the interesting part of this case. This woman was obliged to remain a very long time in the ward, suffering from multiform accidents. When she was admitted, some thirty days had elapsed since she had taken her poison, and her urine was laden with arsenic. Soon after, the elimination of arsenic stopped. I then gave her iodide of potassium, and under the influence of this treatment, the elimination of arsenic commenced anew.

Here, however, is the really interesting point in the case. This woman had been admitted in the middle of the month of October, 1864; on the 16th of May next following, I had her hair cut; that hair contained an enormous proportion of arsenic—at the end of eight months.

Now, you know what are the interpretations given to the

phenomena connected with the storing away of poisons. No very clear idea seemed to prevail as to how they could accumulate; it was said that poisonous substances, especially the metalloids, were generally found in the parenchymas, especially in the hepatic parenchyma. But no one attempted to explain how, or why, this accumulation in reality takes place. It takes place in the histological elements themselves.

Arsenic first locates in the plasma; it then forms a part of the histological elements. That is so true, that, at the expiration of eight months, the hair was full of it; now, it evidently could not have penetrated there except through nutrition. This is the only allowable interpretation that can be offered, as there is nothing in hair, except the cells, which, when united, form hair.

Besides the manifestation of mechanical effects, of which we have given you some examples, besides the chemical effects which we have just recalled, medicamental substances, in their manner of acting, present phenomena which are connected with molecular physics. These are the effects which I propose to name *dynamizing*, and which remind us of what the imponderable fluids produce.

You all know what, by general agreement, are called "endothermic" substances. They are compounds, in which heat, as we formerly expressed it—at the present day we should speak differently—is, as it were, imprisoned in a latent state.

These bodies are very numerous, for we may say that latent heat is contained in all bodies; but there are a certain number which contain a great deal more than others. I need not insist upon it—you all know what a quantity of latent heat exists in water; you know the sum of the caloric which it gives up when it solidifies. Well, there are a great many bodies which likewise contain heat.

I stated, awhile ago, that that expression was a good one before the doctrine of the correlation of forces was understood. At the present day, we would call them *dynamized* substances. In fact, those substances do not always yield up heat. Here, for example, we have a concentrated solution of sulphate of soda; it is

saturated, and crystallization rapidly takes place. While it crystallizes, as in the case of water, there is a considerable elimination of heat; in this instance, it is heat which is disengaged.

Now, we take and dissolve arsenious acid: the solution is saturated. In the dark you will observe that phosphorescent rays are disengaged; the phenomenon is of the same order as the one before mentioned, only, in the present case, it is under the form of light that part of the force is disengaged.

A similar re-action takes place when arsenious acid passes from the vitreous to the opaque state; that is, where, from amorphous, it becomes crystalline.

Many instances thus occur in which heat, light and electricity are produced. These are well-known facts at the present day, and to dwell merely on those which particularly interest us, let me tell you that those mineral waters which rise from the bowels of the earth, possessed with a particular constitution, which has secured for them the name of "vitalized waters," carry with them to the surface, not only heat, but electricity; so that, even by means of instruments of no great delicacy, the presence of both can be demonstrated, as has been shown long ago by Scoutetten.

It thus becomes evident that those bodies which are endothermic, are, in reality, charged with forces, which they yield up under the form of heat, chemical action or light.

You know what are "fulminates;" that is, metallic nitrates: they are highly changeable combinations.

It is because of the weak affinity which nitrogen has for the metals, that under the influence of the least shock those compounds detonate, and liberate forces of matchless potency

There are, therefore, a great variety of forms under which force presents itself. Well, this force which I have just shown you as imprisoned in endothermic bodies exists in variable degrees in what we call medicaments, particularly in the alkaloids, and in a certain number of neutral bodies.

Only, herein lies the difference between fulminates, like dynamite, for instance, and the molecules of medicamental substances;

that while these surrender their force slowly, steadily, and without shock, gun-cotton, and the nitrates yield up theirs in a violent manner.

In conclusion, while the substances of which we were just now speaking, may be considered as Leyden jars of excessive power, medicaments are, so to say, magnetic bars. But there always exists a surrender of force. And under the influence of this yielding up of force produced by the medicamental substance introduced into the economy, structural modifications take place in our organs; our tissues may be said to pass under real allotropic conditions; that is to say, they are either charged, or again, more or less exhausted, reminding us, in the former case, of ozone (O^3) or in the latter simply, of ordinary oxygen represented by O.

What I say to you here is not merely a guess or theory; it is at this day a demonstrated fact. I stated, upon observing that sulphate of quinine, without undergoing transformation, had saved from certain death patients impregnated with marsh miasma, that it must have yielded up force, it must have passed into an allotropic condition.

Mr. Guyochin, analyzing the alkaloid which was present in the urine after having passed through the organism, found that it was no longer quinine, but quinidine and quinicine; that is to say, quinine which had lost its force and was reduced to impotency.

Here is, therefore, an experimental proof in favor of the doctrine which I have developed to you.

CHAPTER II.

General Therapeutics—[Continued.]

SPECIFICS IN THERAPEUTICS: The doctrine of signs—lungwort, carrots, albuminates.

Dynamizing Action: Alkaloids, glucosides, tea, coffee, coca, maté.

CRITICISM OF THE EXPRESSION "Tissue-saving medicaments," or agents limiting waste.

THEORY OF ORGANIC FORCES: Examples.

Adynamizing Actions: Tonics, stimulants, radical forces, and acting forces. Variability of effects in tonics and stimulants, strychnine, morphine.

EFFECTS OF MEDICAMENTS: Physical, chemical and organic. Preponderance of the organism in the effects of medicaments. Positive and negative, direct and indirect, transitory and durable effects, (*alteratives*). Arsenic.

GENTLEMEN:

I have told you that in medicaments we have to study elementary actions, independent of the effects produced by these actions.

Formerly, matters were not so difficult; medicaments were endowed with peculiar virtues, they were considered as *specifics;* under these circumstances it was not difficult to understand their mode of action. It was supposed that nature had endowed certain plants with properties which rendered them apt to directly battle against disease, as though a single combat had taken place between the disease and the remedy.

A *doctrine of signs* had even been invented, according to which nature was supposed to have inscribed upon the different productions of the vegetable kingdom the various ailments for which the medicaments at our hands were suitable.

Thus the spots in the pulmonary or lung-wort indicated the use to be made of that plant in tubercular phthisis, because in

that disease the lungs are crammed with something that resembles these spots. In the same way carrots were indicated in cases of icterus.

At that time it was not difficult to understand the mode of action of medicaments: they possessed properties. They cured *proprio motu* by something that could not be explained by the laws of matter.

With us, we are made to pause, and obliged to master much more difficult details in order to understand the mechanism of therapeutic agents.

I have shown you that even in medicaments, that is, in substances which we administer, there are mechanical actions; and I have given you examples of these. But chemical actions are the most numerous; at times it is a simple chemical combination with the bodies existing in the organism, as when we free the stomach from acids by the use of alkalies; again the combinations are with the tissues themselves, as when we produce, for example, cauterization.

Finally, in other instances, the combinations are of a somewhat peculiar nature; they no longer are the definite combinations with which you are acquainted, but combinations of the kind designated by the name of *albuminates*.

You are aware that a great number of substances are considered as entering into combination with albuminoidal matters; well, analogous combinations take place between the albuminoidal matters in the body and medicamental substances. At a later period those substances go towards forming a part of the tissues; either, if normal, they become simple elements, or, if they are simply analogous to the normal substances, they enter and substitute themselves for these substances.

These are the different kinds of chemical actions which can be produced by medicaments. When we last parted we were considering dynamizing actions. I desire to add this much, that by means of those substances which are capable of yielding up force, we succeed in dispensing the organs from the necessity of producing it.

The organs, as you know, produce force. Take for instance the muscle, the physiology of which is well known. It is obliged to burn not perhaps its own substance, but the residuum of denutrition, and it does so to produce force. If it does not do this, it lacks the necessary force to contract itself. Now, endothermic substances are capable of supplying to the muscles and to the nervous system the force which they would be obliged to produce in order to act.

This opinion seems to me, and I tell you so in advance, applicable to a great number of medicinal substances. For example, the alkaloids, and the analogous principles which are neutral bodies, glycosides, those substances endowed with such immense power, that in almost infinitesimal doses they produce enormous effects ($\frac{1}{4}$ of a milligramme, as in the case of aconite), seem to me especially to possess this *dynamic* action; that is, they seem, in the selection they make of certain parts, to be specially capable of supplying strength and of exciting the nervous system.

At any rate, this seems demonstrated, as far as a certain number of principles are concerned, which belong as much to hygiene as to therapeutics. I have reference to those principles which exist in *tea, coffee, coca, maté, etc.* These substances, at present, are admitted by a certain number of physiologists, among the substances which are capable of supplying strength.

A French agriculturist, Count Agénor de Gasparin, some thirty years ago, called attention to the singular property possessed by coffee, the best known of those substances in France and Belgium, of sustaining strength, while it contributed but very little ponderable substance. He pointed out that the laborers working in the coal mines of the Ardennes, ate but little, but with coffee were able to produce enough strength for their work in the mines. This disagreement between the small quantity of substance introduced for consumption, and the amount of force produced has called attention to new properties which were but little thought of. But there was difficulty as to the interpretation. For a number of years certain expressions, which I con-

sider absolutely defective, have crept into scientific language; these wordings claimed to express the manner in which the above phenomena took place. Thus such substances have been designated by the name of "tissue-saving foods," or by the univocal expression of "*anti-deperditeurs*" (anti-deperditives). This is not new, although it was offered as such at a certain period, during which it was considered as a sort of revelation.

These denominations originated in the manner of understanding certain physiological and physio-pathological phenomena, the study of which already dates back over fifty years. W. Böcker was the first to observe that in our therapeutic arsenal there are a certain number of substances capable of arresting the movement of disassimilation as well as that of assimilation.

In his opinion and that of his followers, they are substances capable of preventing organic denutrition. I believe myself able to show to you, that this method of speaking is as defective as is erroneous the idea upon which it rests.

We shall see that to spare our organs by this process, to save ourselves from the need of increasing our resources by another alimentation, this is not properly the way to save. As to "anti-deperditives," it is again a still worse denomination, because it would seem as if they were satisfied with the word, and believed that after saying alcohol is an anti-deperditive, they had unfolded a whole doctrine. I shall render palpable to you all that this method of comprehending the phenomenon is absurd. And this opinion, which I was first to express, has finally been adopted by a certain number of right-minded persons.

Nothing is easier than to diminish the organic waste, and consequently to slacken the denutritive movement of the organs. We have only to suppress all excitants, intellectual excitants among others; we can place ourselves in darkness, make use of stupefying agents; by such methods we can diminish losses; is it a way, however, of acquiring strength? No; it is only the way not to expend any. But, as it is only by means of respiratory combustion that we arrive at producing the strength necessary to our activity, it is evident that those who would sub-

mit themselves to this anti-deperditive regimen, would sink to the condition of certain nervous women in the Salpêtrière. They drop into a species of imbecility attended by torpor, and become motionless, like Hindu bonzes.

From this you understand that it is impossible to attribute the name of anti-deperdition to such marked effects as those from coca, which enables Indians to travel a long distance, relying only upon a small quantity of this substance; or to those of coffee, which allow us, when occasion requires, to make use of great cerebral activity, without taking any more food than at ordinary times. This stimulating action in substances like tea, coffee and coca, can only be accounted for by a contribution of strength; for this reason I have called these substances *dynamizers* or *dynamophores*, if you prefer it, the former word being already used in another sense.

The question is to know what sort of force these substances supply us with. They furnish us with no other forces than those of the chemical substances themselves, be they organic or mineral. Only, we must here introduce a new idea; it is that of the correlation of the physico-chemical and organic forces; and I shall ask your permission to develop somewhat this view, because were I not to do so, I might be taxed with wishing to place life in an equation with heat.

That is, however, what has been done in a certain number of documents, in which it was repeated that when I spoke of the correlation of physical and organic forces, I meant to say that with the aid of the physical forces, life could be engendered. I do not believe this: it is not in this way that I understand the question. As scientists, we must acknowledge that in living beings, independently from all organization, there are forces which belong to brute matter. But there is something which is absolutely irreducible, it is formation, nutrition, that force which the ancients designated under the name of *vis formativa*, and to which the most ancient philosophers gave the name of ενορμον, the force which causes the organs to develop, and which enables the eye of the salamander to reproduce itself. That force, how-

ever much I seek, I can find no way by which to reduce to chemical combinations, or to the action of imponderables. In living beings what is absolutely individual to them is reproduction and nutrition, which are one and the same.

As Aristotle had said, as Lallemand (of Montpellier) has at a later date demonstrated, to the foregoing something still more irreducible must be added; that is, *thought*. There, again, as a scientist, I am at a loss to understand, and I turn from that field which is of such difficult approach. But I claim that there, as well as in nutrition, in the genesis and repairing of the organs, qualities, and faculties are found, which belong solely to the living beings of all kingdoms, and that those faculties are absolutely irreducible to the action of inanimate matter. Hence it is not of these I shall speak; but there are other faculties which belong to certain forms, to certain structures of organized matter, which are not irreducible to the laws of physics. Such are, for example, the muscular and nervous forces, *myotility* and *neurility*, names coined by Charles Robin, and that property possessed by the globules of the blood of taking up oxygen for the purpose of yielding it again.

Those properties are not essential to living beings in general; they are met with in certain beings, but are not everywhere found. They are not, consequently, indispensable to life; they are, on the contrary, attached to a particular structure, and so long as this last exists, these properties are not found wanting. So long as the structural properties exist, the qualities, the functions of that structure persist. I have had, in former times, unquestionable examples of this, which it gives me pleasure to recall. On one occasion, at the Necker hospital, I had to complete the amputation of a limb which had been crushed. I separated the arm from its attachments. I was then tempted to examine what was going on in the biceps, which, although stricken by death, had preserved its warmth. Out of the muscle I carved cubes, and I endeavored to produce a contraction in them. Nothing was easier, and by the most varied processes: by blowing upon them, by pricking them with a scalpel, by the

use of a battery formed by a silver and copper coin. After a time the contractions would cease. I would take up another, and commenced anew. I then returned to the first, and again obtained results. This lasted during three-quarters of an hour. It proves to you that, even when deprived of life, this substance was still apt to perform its functions; that is, force could transform itself into action, and consequently into mechanical contraction. But, as I have observed, this force would become exhausted, and it was necessary to give the cubes rest before obtaining another series of contractions. This is quite analogous with what exists even among mineral substances which owe to their structure qualities that are not inherent in their chemical composition. Take globules from an animal, they are quite different from those in man; but, provided they are not any larger, they will behave, in the human circulation, in exactly the same manner as the blood globules of man; and these globules preserve the property of favoring the exchange between oxygen and carbonic acid during all the time that their existence lasts under a certain particular form which constitutes a structural condition analogous with that of crystallizable mineral substances.

Well, those organs which have particular properties attached to their structure, can be charged by substances such as the aliments, foods or medicaments I mentioned a while ago, in the same way as they can be charged by the aid of electricity.

Let me, in a few words, tell you of one instance which can be classed under this head, and which is likely to convince you. I once had under my care at Beaujon, a patient who had taken a sudden cold, from which paralysis of the left arm had resulted. He was admitted quite shortly after the accident, and when I was called upon to examine him, I found that not only had he lost all voluntary movement in the upper left limb, and in that only, but also that electrical irritability was nearly all gone; I could barely cause the biceps to harden a little. Under such conditions as loss of voluntary movement and almost total extinction of electrical irritability, it occurred to me to say to him, while the current was passing: "Why don't you carry your

hand to your chin." He replied, laughing: "You know full well I cannot do so." He was resisting. Finally he did as I asked him. I got him to renew the movement as often as I pleased; all that was necessary was to allow the current to continue.

While he was performing that movement, I withdrew one of the rhéophores; his arm fell back, inert.

What was taking place? Matters were only a day or two old. Evidently the muscle had suffered no alteration; only it was no longer producing force, it was incapable of causing a contraction. It possessed structure; I gave it force again by means of electricity. These facts are far from being as singular, or as strange, as they appear at first sight.

It is not very rare to observe, during the progress of certain diseases, cases of paralysis happening, in which the will loses its efficiency, and inductive currents become useless, but where the combination of these two agents, current and will, determine motion.

Thus, I have often observed, and especially on one occasion, in company with Dr. Bonnefin, cases of complete facial paralysis attended with impossibility of winking the eye. But during the passage of a continuous current—it is the best in such a case—the patient could close his eye.

When he tried to close it without that, he could not. The current charged the muscle, and the will interposed to have the movement executed.

These phenomena which I point out to you, that is, the return of force, and the calling into action of that force, under the influence of the will, these are facts which, to my mind, leave but little room for doubt, and which demonstrate that either by the aid of substances charged with great energy, such as alkaloids, or by means of other substances which are as much within the province of therapeutics as of hygiene, we succeed in communicating force to organs which no longer produce any.

But it is especially the imponderable fluids, such as electricity,

which manifest, in the highest degree, this power of imparting force to those organs which stand in need of it.

If almost all substances contribute force, there are some, nevertheless, which seem to withdraw it. In the exchanges which are made, there is, at times, a loss.

A while ago I spoke of imponderable fluids bearing force; heat will also bring some, but it must be, so to say, positive heat, that whose intensity is greater than the heat of our organs. On the contrary, if we have to deal with a temperature indicated by the sign *minus* (—), it is evident it will rob us of force.

Now is the time to have you grasp the distinction which is to be established between *tonics* and *stimulants*. You will find that here there is confusion on all sides. You will be told alcohol is a tonic and a stimulant, two words that are actually in conflict.

In speaking to you of those substances which contribute force, I have given you the true theory of tonics. We are to consider as tonics, those substances which are capable of increasing the "radical" forces, (to distinguish them from acting forces,) as the ancients called them. This distinction between radical and acting forces is an absolutely just one, and it should be retained

Stimulants call organic activity into play. Every living organ is endowed with excitability; that is its most general property. Anything can be a cause of excitement for most tissues; and stimulants are nothing more. You see that this is a great way from increasing the supply of forces.

While tonics are means by which we enrich ourselves, stimulants are, in reality, means of impoverishment. I hasten to add that, in other ways, tonics and stimulants produce analogous effects.

Take, for instance, strychnine: when but very little is used, the excito-motive power is increased. Give it, for example, to a paralytic patient, you supply him with the means of raising his body, when, otherwise, he could not do so; he can produce a greater number of efforts. But if you go beyond the due measure—if, rather, too heavy doses are given—it is no longer an increase of radical force that is produced, but a real excitement.

Likewise, and inversely, I will mention opium, which, in small doses, is a stimulant, and which, although a stimulant, becomes an indirect tonic, owing to the vascular excitement which it determines in the organs.

I have now reached the effects of medicaments. I have told you of their elementary actions; these are mechanical, physical or chemical; all this is understood. But the effects they produce upon the organs should be the object of a distinction, which, so far, has not been made.

Among the effects, the same divisions are to be established; that is, they either are physical, chemical, organic or vital. As an example of physical effects, you may have recourse to cold. As a chemical effect, you can modify the alkalinity of the blood by giving or withholding alkalies.

Ordinarily, the effects obtained are of a higher order, being organic or vital; and these effects may also be produced by mechanical and physical methods. Thus, cold not only reduces the temperature, but determines the retraction of the vessels and the corrugation of the skin. It may be said that almost always inferior mechanical agents, or those simply endowed with properties belonging to general physics, cause, within us, phenomena which are, properly speaking, of a very elevated organic order, and even phenomena of a vital order, since, by indirect action, they are able to render nutrition or disassimilation more active.

Upon the whole, if we consider these effects which are common to almost all agents, and which have no connection with their nature, we find that those agents are really only an occasion for the manifestation of the phenomena which take place in our organs; and that they behave with regard to those more or less complicated apparatus, such as the nervous system, in about the same fashion as the finger, when it touches off a piece of machinery. When you fire off a gun, it is not your finger which causes the force of the phenomenon, no more than when you ignite gunpowder.

There now remains to be made a distinction with regard to the effects of remedies and medicaments.

There are effects which take place immediately after the application of the medicament or remedy, and there are others which are, so to say, the negative of these, and which are the result of predisposition. Thus, when a cold douche is thrown on the surface of the body, we notice that the patient, who may have been rose-colored, becomes pale the instant the water is projected on his body; and if it was not water, but cold air, you might ascertain that the patient had grown cold; you also notice that he is all gooseflesh, and that the parts have shrunk. But this is only for an instant. If you wait a few seconds, you see inverse phenomena take place, redness returning, the capillaries dilating, the gooseflesh disappearing, and in place of the chilliness an exaggerated calorification is manifested.

What takes place there on the surface, under the influence of a physical agent, also takes place in the interior under the influence of medicaments. They give rise to phenomena which are direct, immediate, positive, and to other phenomena which are different and due to the re-action of the organism. The immediate phenomena I propose to call *positives;* the other phenomena *negatives* of the remedies. The latter are also very positive, but nevertheless they seem to be the negative of the phenomena proper. To sum up, I will remind you that medicaments and remedies may simply produce excitation, that is, perform the part of the spur with regard to the steed, and determine the calling into play of nervous movements, or their acceleration if the movements already existed. But in many circumstances they are also the means of integrating force, and they are then what I have called *dynamophores.* Finally, in other circumstances, medicaments introduced into the interior of the organism behave by virtue of purely chemical actions, and they form combinations. This is a third and very frequent mode of action.

But there is a fourth one, which is very interesting; it is this: There are substances which, in place of merely traversing the organism, form combinations with the plasma, penetrate into the substance of the elements, live the same existence as those elements themselves, and as long as they do, and consequently

during a certain time, form an integral part of the organism. These are called *alteratives*.

Among those medicaments there are some which are real aliments; for example, iron, sulphur, manganese, cod-liver oil; but there are others which are only analogous with the substances which enter into the normal constitution of our organization, as, for example, arsenic. This substance seems to take the place of a certain proportion of other substances which normally exist, and which resemble it.

In the first lesson I could have mentioned experiments made by my learned friend Mr. Paul Thénard, which prove that in the bony corpuscles the triple arseniate of calcium may take the place of the tribasic phosphate. Do you notice it—arsenic and phosphorus two nearly-related bodies? These experiments repeated a certain number of times upon animals fully confirm the law which I pointed out to you in the preceding lesson.

CHAPTER III.

General Therapeutics—[*Continued.*]

Correlation of Organic Forces—The organism makes use only of the natural forces; application to the action of electricity.
All medicinal action reduces itself to an exchange of matter or of force.
Importance of the organic substratum. Ergotine and strychnine.
Cause of the election of organs by medicaments.
Physico-Chemical Constitution—Phosphorus, phosphates of the alkaline earths, arseniate of lime, iron, salts of potash, introduction of medicaments, alcohol.
Affinity of the Histological Elements—Alcohol, ether, lecithin, protagon, myeline, cerebric acid, alkaloids.
Physical reason for those affinities—dyeing by coloring substances.
Differences in Organic Sensibility—Extensor and flexor muscles.
Means of Elimination of Medicaments.

MINERAL SUBSTANCES: Chemical composition.
Perfect—Sulphate of soda.
Imperfect—Oxalates, cyanides, chlorates, chlorides, iodides, bromides, arseniates, salts of iron, salts of copper.
Ill-defined Combinations.
Unstable Combinations—Hyposulphites, hypochlorites.

GENTLEMEN:

The new method of interpreting facts, of which I spoke in the last lesson, supposes a close correlation between the physical and organic forces, since a substance taken from inanimate nature is capable of yielding the necessary force for the support of life.

Force is linked to a certain material constitution of the organs. For example, in the globules of the blood in the muscles, in the nervous reticulations, and in the medullar and cerebral substances, there are functional actions which in the main, only depend upon the forces of nature in general. I have given you

instances which to me seem of a kind that should carry conviction to your minds. I have shown you, for example, that an electrical current could, for the time being, bring back *voluntary* contraction to an organ that had lost it. This return is absolutely instantaneous, it lasts as long as the passage of the current continues, and disappears at the very instant that passage ceases. But I omitted to lay before you, at the time, the different methods of interpreting that phenomenon.

Evidently the opinion might be advanced, that by the aid of an electric current you have simply charged the muscular elements with extra force, and under those exaggerated conditions you have given occasion to rather more active manifestations of organic functions. But it is very difficult to understand by this process the instantaneity of the phenomenon. No sooner are the rhéophores applied, than under the influence of the will the muscle contracts itself. This instantaneity does not correspond with the idea that those are mechanical or chemical actions, called into play by the influence of the current. However, two other hypotheses may be made, both in harmony with the doctrine of the correlation of forces. One of these hypotheses was offered to me by my learned friend, Mr. Berthelot; it is the hypothesis of *relays.* You know that in the case of a very long electric wire, when deperdition takes place readily in a foggy and damp atmosphere, it becomes necessary at the end of a certain number of kilometres to set up another electric machine, so as to facilitate the passage of the current; these are what are termed *relays.* Thus in rainy weather it is necessary to have relays between Paris and Rouen.

It might be admitted that, under the conditions of which I spoke, that is, when the upper limb had been paralyzed, there was a certain degree of inconductibility in the nervous branches, and that, under the influence of the current, the movements might be communicated from the centre to the extremity of the nervous branches, brought in contact by that extremity with the muscular fibres.

The other hypothesis, in favor of which I had decided, rests

upon the possibility of restoring to a muscle, no longer making any, the force that it should have made.

Whichever of these hypotheses is adopted, we must always acknowledge the correlation of physical and organic forces. Medicamental substances, and very often even remedies, (for imponderables are not medicaments,) act by yielding up force to the economy, or by giving matter to it. There results from this, that in the conflict between medicaments or remedies and the economy, the latter receives or loses either force or matter.

At first sight it will appear strange to you that it is possible to explain this indefinite diversity of medicamental actions with that uniformity of process which I suppose exists. You will soon see that it is not difficult to harmonize facts with this view. In the first place, I would have you remark that as regards the diversity of the phenomena which we observe, it can be explained by the positive and negative effects of the remedies; that is, by the actions they produce, and the re-actions of the organism.

But you will understand that it is especially easy to comprehend their actions when we consider the multiplicity and diversity of the organs.

In fact, whether medicaments give force, and in consequence are *tonics* and *stimulants*, or if they in general are *excitants*, this is of but little moment, since at times they excite the sensory nervous system, and at others the motor system is concerned. They address themselves now to the special senses, then again to the general sensibility, and so forth.

As motor stimuli, here are, for example, ergotine and strychnine, which are potent agents on the motor system, and which probably act by giving force. But ergotine addresses itself to the motor system of organic life, to the smooth fibres which animate them. On the contrary, strychnine addresses itself to the medullary portion. Consequently, while ergotine produces a contraction of the bronchiæ and of the uterus, strychnine produces an exaggeration in the intensity of force manifested by the muscles.

You see that, although the mechanism is identical at bottom,

by the mere fact that medicaments address themselves to different organs, the effects are different. I will render these facts far more intelligible to you by making this hypothesis: suppose one medicament is capable of acting on the vaso motor constrictor nervous system, and another on the vaso-motor dilator, (you know that at the present day this division is by authority; it was admitted by Cl. Bernard, and is by Vulpian,) if we suppose an effect of the same, an excitation, a cession of force being exercised on each of these two systems, the effects will be diametrically opposite.

If you excite the dilator, a hyperæmia will be the result; if, on the contrary, you excite the vaso-constrictors, the consequences will be ischæmia or anæmia, and all its phenomena with which you are so well acquainted.

You therefore see that by the same process, with the same manner of acting, according as this action is applied to different organs, you will obtain the most varied effects. I deem it unnecessary to adduce any other examples.

The question here presents itself: Why do certain medicaments address themselves to a region, an organ, a portion of an apparatus, and why do others address themselves to other organs and other apparatus? Why, for instance, has opium its elective seat in the encephalon? Why does strychnine address itself particularly to the medulla? Why does aconitine act on the expansions of the nervous system? And why does ergot act on the uterus? I make no pretence at being able to give the reasons for these elections, but there are certain rays of light which can be projected upon this portion of the scientific field.

I would have you remark that what governs the direction taken by remedies is, in the first place, a sort of predestination, which is attached to their *physico-chemical* constitution, and which causes these remedies to go and take their place, each in a particular tissue, and destines them to be eliminated by certain ducts. I repeat it, these predestinations are in connection with their physical and chemical qualities.

Why is phosphorus a stimulant of the nervous system, or, as

it is termed, a *nervine*, for this is the univocal expression employed to designate its action? Why, being a nervine, does it produce effects which at times are useful during the course of diseases, such as paralysis, and the different forms of tabes? The reason for this is very simple.

If phosphorus addresses itself to the nervous system, it is because it is one of its constitutive elements, consequently it is very natural for the nervous system, on finding more phosphorus present than is contained in the food, to make use of that phosphorus, and have its nutrition thereby heightened. If there is too much there will be excitement. Here, now, are the phosphates of the alkaline earths. Why do they modify the bony system in cases of rachitis and osteomalacia? Why do they heighten nutrition in cases where it is languishing, as with anæmics and cachectics? The reason is simple. Because they are an indispensable element in the constitution of the bone corpuscles. Why do they awaken nutrition? For the same reason.

There are experiments proving the effective and necessary intervention of the phosphates of the alkaline earths in the development of all tissues, not only of the animal tissues, but also of the vegetable. It is, indeed, already a very long time ago, that my learned colleague, Mr. Gosselin, in company with a naturalist, young at that time, Mr. Alphonse Milne-Edwards, made experiments upon animals and vegetables which prove the intervention of the phosphates in nutrition.

Wherever there is a cell, it may be said that there is a certain proportion of phosphates of the alkaline earths; it is, therefore, natural that these phosphates should go to cells in process of development. Arseniate of lime may take the place of the phosphate in the bones. Why is this? Because arsenic and phosphorus are elements of the same group. We come now to iron: why does it go to the globules? Why does it help to increase their number? Because iron forms an integral part of that coloring matter found in them, and thus is one of their elements, the same as manganese.

You see from this alone, that it was predestined to act on the

blood particles, and consequently to restore them in the organism of anæmic or cachectic persons.

Now, a word on the salts of potash. These salts have some special effects which enable us to make use of them in certain morbid cases. When they are used in moderate doses they act as stimulants of respiration, and of the muscular function. Why this action on the organs of hæmatosis, and on those of contractibility? It is because there naturally exists in the blood globules a notable proportion of potash salts, and that these same salts are to be found in considerable quantity in the muscles of which they constitute, so to say, an integral part. Owing to this, they are aliments for those special organs. Consequently, you see of what importance salts of potash are in anæmia, in saccharine and albuminous diabetes, and I may also add in polysarcia, for gout, polysarcia, albuminuria and saccharine diabetes, all belong to the same morbid family.

Under those conditions, potash salts awaken activity in the globules, consequently they favor the functions of the muscles, and on that account, also, allow those which are overcharged with adipose tissue to burn more actively, since circulation is under better conditions.

These are examples which, I think, prove to you what is the condition which directs the different medicaments towards such or such an organ, and which assigns to them in advance the function to be filled, either in the physiological or morbid state.

As to the substances which do not act the part of food, which do not remain in the economy, but which, so to say, only pass through after having produced the different very fugitive phenomena which I pointed out to you, what circumstances determine the direction taken by them—the spot towards which they will aim their blows? Here they are: In the first place, there is the point of application of substances not called upon to perform the part of foods. It is evident that if you apply a substance on the gastric mucous membrane, you will develop by contact certain phenomena, which precede all absorption, and which are in relation with the anatomical character of this membrane.

Do you want an example? You introduce into the stomach of a person in a fainting fit a certain quantity of an alcoholic liquid. This liquid, by contact alone, determines the re-awakening of all the functions, reflex action, sympathy, as the ancients called it, and that, too, before the liquid has had time to be absorbed. This is an effect which is due to the point upon which the medicament has been applied, for, it stands to reason, you might have placed it on the sinciput without obtaining the same result.

But there are circumstances of far greater importance than this; these are the chemical affinities which exist between the medicaments and the histological elements, and which then decide on the point where an accumulation of the medicament will be made, and consequently towards which its principal effects will be directed.

I will return to this before I leave the subject.

I desire to add, right here, that there is another circumstance which also determines the election of medicaments; I refer to the passages for their elimination. They are eliminated some by one passage, others by another, and I will show you that on their way they determine more or less noteworthy phenomena.

I come now to the question of chemical affinities between medicaments and histological elements. Long since, medico-legal physicians observed facts which relate to this question; long ago, my very dear friend Tardieu,[1] called attention to the smell of alcohol exhaled from the brain of men who had died of acute alcoholism. Since then the smell of ether has been observed in persons who had died from etherization. To what is this due? I have advanced the opinion, which is confirmed, as you will see by other considerations and other facts, that alcohol, which is capable of dissolving a certain number of sub-

[1] Tardieu, *Medico-Legal Observations on the Inebriate State*, considered as a complication in wounds, and as a cause of prompt or sudden death. *Ann. d'Hyg.* 1848, *t. XL., p.* 290. And *Medico-Legal Studies upon Wounds*, (*Paris* 1879,) *p.* 109.

stances in the nervous system, attaches itself to it exactly as water impregnates substances that have an avidity for water.

This same fact has been noticed under another aspect, and indicated a long time since by a great chemist, who committed but one fault—that of having become a great manufacturer—Justus Liebig.

He called attention to the fact that the intermediate alkaloids between the fatty and resinous bodies seem to address themselves particularly to the nervous system, and that in the nervous system essential substances are met with which seem to play a considerable part; like Mr. Fremy's cerebric acid, a substance which is a fatty acid.

Liebig remarked that this predilection of the alkaloids for the brain seemed to be connected with their analogies of constitution with the immediate principles of the nervous system. He observed, in fact, that the alkaloids are bodies not far removed from the fatty bodies.

What Liebig said of cerebric acid might be applied at this day to other substances none the less essential to the nervous system, and in particular, to Gobley's *lecithin*, to O. Liebreich's *protagon*, and to the myeline of the nervous tubes.

You understand, therefore, why it is that the alkaloids address themselves more particularly to those organs containing substances with which they have a greater degree of affinity; they are, so to speak, the solvents of these in the same way as alcohol and ether are for the fatty substances in the nervous system. But we do not yet know why it is that a given alkaloid selects a given portion of the nervous system; opium, in particular, the cerebral hemispheres, strychnine the medulla, and aconite the divisions of the fifth pair. It is highly probable that this is owing to chemical affinities of the same order as those to which I called your attention not long ago.

This affinity is not any more extraordinary than that daily observed among icterics. To what is due this coloring by hemapheine, or by the coloring matter in the bile? It is due to a positive affinity presented by those substances for the fibrous

tissue, for it is in this tissue that the coloring takes place. It is, so to say, a kind of organic lake, which is formed by the tissue and the coloring matter; exactly as you see certain coloring matters attaching themselves, from preference, to silk, and others to vegetable cellulosis. You constantly see this in micro-chemistry. Why are solutions of carmine and of nitrate of silver used? Because these chemical substances have a particular affinity for a certain class of elements, for at times only the core is colored. It is the same with iodine for glycogenous matter.

Suppose that those substances which are inert, which thus attach themselves to a certain order of elements, were at the same time active substances: it is clear that, thrown into the circulation, they would produce upon the elements considerable changes in their structure and in their manner of operating. Thus there is no difficulty in understanding those phenomena, which, however, are not as yet demonstrated.

There is another point to be noticed. When we study the undivided action of medicaments or poisons (they are all the same, only differing in doses,) we are not long in noticing that their effects make themselves felt, by preference, on a certain division of the nervous system: thus, sensibility often escapes, while movement is affected, and that, too, more in certain regions than in others.

For example, you give a medicament capable of producing paralysis; whatever is the nature of this agent, where will it, in preference, make itself felt? on the extensor muscles of the forearms and of the lower limbs. Is not this something very strange? And here the fact is to be explained, not only by chemical affinities, but by organic predispositions.

It is the same for the sensory system. Phenomena of sensibility persist by virtue of an anatomical circumstance which has not been sufficiently noticed, but to which I call your attention. Sensibility does not only exist where there are sensory nerves. Are you not aware that on the back of the hand there are but few nervous fibres? Yet there is not a single point where in pricking yourself you would not feel the sting of the needle.

What is this owing to? for it would be purely accidental had one always met with a nervous fibre. It is that the histological elements of the dermis are all endowed with a faculty, which is excitability, and that when their excitability is called into action, an excitation is gradually established among the histological elements which are in contact. This is what Hunter termed the sympathy of continuity and contiguity. When this disturbance has reached a sensory filament, the latter communicates it to the nerve centre, but it has not originated in this. In other words, transmissions of sensibility are not only made by nervous filaments, but also by surfaces. That enables you to understand how, even when there is the lesion of a nervous filament, there still remains transmission of impression, because it is transmitted by routes which are not indicated by nerve filaments and tubes.

It is entirely different as regards mobility, which is connected with nervous ramifications in such a way that voluntary movements can only be transmitted by nervous filaments. Why this difference of action upon the extensors and the flexors? A much greater difference than is supposed, and such that I was able to say, in times past, what has since been admitted, that there must exist in the nerve centres distinct regions for the muscles which extend, and those that bend the body. Well, the region of the muscles which extend is a region far more sensitive to all exciting or depressing agents than the region that governs the muscles which flex the body. And it is because of this predominance that when you introduce strychnine, you produce convulsions in the muscles that flex and not in the others. In order to impress upon you these phenomena, I have but to say to you that this predominance of force manifests itself even in intra-uterine life; to it is due the curved position assumed by the fœtus in its mother's womb, and this predominance continues throughout the whole of extra-uterine life.

Now, a word upon the influences exercised by the passages for elimination on the mode of action, and the elections which medicaments make in connection with certain organs. Why do the

essences—like essence of turpentine, of cajuput, of eucalyptus—exercise their influence upon the respiratory passages or on the skin? It is because they pass through the respiratory passages and traverse the sudoriparous glands, and that on their way they produce the effects of which they are capable.

Why does copaiba produce such marked effects upon the urino-genital apparatus? Because it passes through the kidneys, and after having been eliminated by these glands it modifies the mucus while on its passage.

Why are cantharides held in such high repute in certain regions of the Orient? Why do they develop a factitious and short-lived power? Because they are eliminated by the kidneys in sufficient proportions to determine phlogistic phenomena.

Chloride of potash is an effectual cure in a certain number of buccal affections, because it is eliminated by the salivary glands and those adjacent.

You thus understand, that in cases of ulcerous membranous stomatitis, it can determine modifications that are favorable to restoring health in the glandular apparatus.

Finally, we have emetine, that is the active principle of ipecac., which, when introduced under the skin, and thrown into the circulatory torrent, leads to vomiting.

Why is this? I am well aware there are two hypotheses; but there is only one which is valid.

The elimination of emetine takes place through the digestive apparatus. It does not act while it is in circulation, but when it is eliminated by the glands of the digestive tube—principally by the liver—it then reaches the intestine, as if it had been directly introduced there, and when the quantity is sufficient, it brings on nausea and vomiting. This fact, at the present day, is beyond cavil. Emetine, when introduced into the stomach, acts energetically as a nauseating emetic, in doses of gram 0.15–0.20. Introduced in the cellular tissue, its action is greatly reduced; it becomes necessary to increase the dose, to gram 0.30, so as to obtain effects. If you experiment upon animals and kill them at the end of a given time, when they show signs of nausea,

you will find present in the intestine emetine, which you can administer to another animal and cause it to vomit.[1]

Here, then, are a number of circumstances showing that the effects of a substance are in connection with the direction it takes in leaving the economy in which it has sojourned but for a very brief period.

I have now reached a very interesting question. It is that of ascertaining (since we have established that medicaments act chiefly from chemical qualities) to what the different remedies owe their properties. They owe them to the nature of the elements which enter into their constitution; to the manner of arrangement of these elements, and also to a particular structure. You know what is understood by structure in chemistry? It is evident that if you simply take oxygen or nitrogen, they act in a different manner. It is the same if you take substances like arsenic and phosphorus; therefore the nature of the elements has a considerable influence on the actions of medicaments. But there is also the manner of combination affected by these elements, and you will see in the next lesson that there are facts of great interest which would be unexpected had they not for a long time been recorded by science. I say that combinations also introduce great differences in the manner of acting of substances which only act as chemical bodies. We may, here, distinguish three cases:

1. Cases in which combination is so perfect that elementary actions disappear. In sulphate of soda it is neither the sulphuric acid nor the soda which acts; it is an inoffensive salt that has a part to perform in the circulation, and which, when introduced in sufficient quantity, produces the effects with which you are acquainted.

2. There are cases in which combination is not so very perfect, but that there is a certain group of elements which will impress its stamp upon the medicament. And here, there are two orders of facts. At times it is a neutral body, at others an acid body, that predominates, or else it is the one which performs the part

[1]. All these very conclusive experiments have been made by Dr. d'Ornellas.

of base. For example, when you have to deal with oxalates, oxalic acid is the dominant, and it is this acid which impresses its stamp upon substances. Hence, oxalates owe their activity chiefly to oxalic acid. Cyanides are in the same category; it is cyanogen or cyanhydric acid which gives them their therapeutic and poisonous properties.

So, also, with the alkaline chlorates and chlorides, the bromides and iodides, with arsenic and the arseniates; in such a way that in all those cases predominance is with the metalloids, which always act the electro-negative part, or with the acids when acting that part; in the other cases it is with the bases.

Whenever, in the place of alkalies, you have to deal with metals properly so called, it is these that in a general way will have the greatest influence over the physiological actions of the medicament. Thus, whatever acid is combined with iron, it is the latter which predominates. Whatever acid is combined with copper, it is the copper; with mercury, it is the mercury. I might add baryta, but it is no longer used, so I need illustrate no further. But there are also circumstances in which things do not happen as I have just stated. It is when we have to deal with weak combinations. It is evident that when you are in the presence of an excessively acid salt, chemically so speaking, you may consider the acid as free; likewise, with very basic salts, you may look upon the base as free.

3. Finally, there are other cases. If you have to deal with hyposulphites and hypochlorites, it is no longer precisely either the acid or the base which possesses influence, but their derivatives. Thus, hypochlorites liberate, on the one hand chlorine, on the other oxygen, and in consequence they act by means of these two elements.

CHAPTER IV.

General Therapeutics—[*Continued.*]

ORGANIC SUBSTANCES: Simplicity of composition.

Nature of Elements—Anæsthetics, hydrocarbons.

The Part of Nitrogen—Exceptions: Picrotoxin, duboisine, morphine, tea, coffee, coca.

Molecular Grouping—Starch, gum, dextrine, vegetable and animal glycose, glycocol, benzoic acid, nitrous ether, nitrite of ethyl, cacodylic acid.

Chemical Composition—Curara and strychnine, apomorphine.

Conveyance of Medicamental Action—Imbibition, capillarity, contagion, reflex action, liquefaction.

GENTLEMEN:

It is the substances belonging to the mineral order that present the peculiarities I pointed out to you in the last lesson. Among substances of organic origin, matters are far from taking place after that fashion. When you consider the disparity which exists in the action of the different substances belonging to the vegetable kingdom, on the one hand, gum, sugar and starch, on the other, alkaloids and glycosides; the one, inert substances, the others possessed of a violence of which we can only form an idea when we think of dynamite; when you compare this greatly varied spectacle, you at once understand that the nature of the elements entering into the composition of those organic substances has but little importance, and that it is the modes of arrangement, the combinations, which possess the greatest weight.

In fact, as you know, organic substances are formed upon three or four ever-similar elements to which other accessory ones join themselves: they are oxygen, hydrogen, carbon and nitrogen. How can we understand that with such simplicity of

chemical constitution there should be such vast differences in their actions?

The nature of the elements in organic substances should certainly be taken into consideration, but I will show you that the most important part rests with the mode of arrangement of those elements.

It has been observed that the compounds which act the part of anæsthetics, and which we make use of in surgery and medicine, are substances which almost all resemble one another, and are very closely allied. They are more or less hydrocarbons, that is, bodies in which one or more molecules of hydrogen may be replaced by molecules of simple bodies, or of chlorine, as in chloroform. But, as a fact, they have always about the same composition—that is, hydrogen and carbon. Those substances, however, all have the property of removing sensibility, and consequently pain. It is possible to go even further, and assert that all hydrocarbons are more or less anæsthetic. You see that the nature of the constituents exercises a great influence.

I will right here give you the proof of this proposition. You all know the effects produced by bouquets of flowers kept within closely-confined spaces. These fragrant emanations are noxious; the gravest results may arise from them, extending at times up to apparent death, if the room is small and the flowers highly scented, as in the case of tuberoses. Well, those emanations are nothing else than hydrocarbons which are being evolved.

The same may be said of the emanations from hops. You have only to lay a child on a bed made of hop blossoms: it will be put to sleep, it will be anæsthetized. Oil of turpentine, of such constant use in the painting of houses, is also an anæsthetic of great power, so much so that men who work in closed rooms, who sleep there, are often the victims of serious disorders. They fall into a state of somnolency, after having experienced headaches and vomitings—in fact, all the phenomena attending poisoning.

Take notice: here again there is hydrogen and carbon. No doubt chemical constitution has an influence here, since there are

but two simple bodies combined to produce the same effects; but there also exists an influence, due to a particular arrangement of the molecules, as you will presently see.

In order to show you what may be the influence of chemical constitution, there remains for me to say that the most active substances are nitrogenized substances; these are the alkaloids. No doubt among neutral substances there are bodies which do not contain any nitrogen, and yet possess great energy, and, in advance, you all have digitalis present to mind; but, at any rate, we must admit that almost all substances of great power are nitrogenized substances.

Chemists admit that it is around molecules of nitrogen that molecules of other simple bodies group themselves so as to produce the arrangement from which will result, for example, a molecule of aconitine.

But here, again, too much importance should not be given to nitrogen, for if nitrogen, as a simple body, exercised a preponderating influence, the intensity of action of substances would be in relation to the proportion of nitrogen in the molecules. Such, however, is not the case. I might mention to you picrotoxine, which is one of the least nitrogenized, yet most violent of poisons.

To this I could add duboisine, an alkaloid obtained by Mr. Petit from an Australian plant, *Duboisia miropioides*, belonging to an intermediary group between the solaneæ and the scrophularinæ; it is a substance allied to atropine, and which, notwithstanding its violence, contains but little nitrogen. Morphine, which is less violent, and which, in place of being given in doses of one milligramme, is used in doses of several centigrammes, contains more nitrogen. The proportion is much greater in quinine and its derivatives. Finally, those alkaloids extracted from substances which I have called dynamophoric, and which are used in therapeutics and as food, such as tea, coffee, coca, are all alkaloids the most nitrogenized and yet the least violent. Thus you see that here, again, we cannot connect intensity of effects with the nature of the elements.

It therefore becomes necessary to interpose molecular arrangement, and especially so when we consider isomeric bodies. For they are not only constituted out of the same elements, but in the same proportion, and yet they are endowed with the most varied properties.

For example, here are starch, gum and dextrine, which have in common the formula of $C^{12}\ H^{10}\ O^{10}$; they are isomeric, but very different substances.

Again, the hydrocarbons, while differing so much from one another in properties, appearance and molecular weight, are all constituted about alike. It may be said that in almost all the essences, from essence of lemon, and turpentine on, the same constitution always prevails—CH, or multiples thereof. Gradually, as these molecules become heavier, the substance is found losing its volatility and gaining in specific gravity. This enables you to understand how molecular grouping exercises its influence on the organoleptic properties.

Here is another example: the two kinds of glycose—vegetable glycose, which is the sugar of certain vegetable products, and animal glycose, diabetic sugar—are both expressed by $C^{12}\ H^{12}\ O^{12}$; but what a difference between those two substances! While grape sugar injected into the circulation of a dog shows itself in the urine, on the contrary, diabetic sugar injected into the same medium will remain in it as one of its elements, exactly as if it had been formed there by the organism itself. But the animal will not become diabetic. The difference is even still greater when we compare glycose with acetic acid; we find the same composition, the same elements in the same relations, and yet what a difference between sugar and acetic acid! Here is a third series: glycocol ($C^4\ H^5\ N\ O^4$), which must be known, because this substance acts a considerable part in very many therapeutic phenomena. When mention is made of benzoic acid, one cannot avoid speaking of glycocol. Well, nitrous ether and nitrite of ethyl have the same composition as glycocol, and may become poisonous.

Here is a more surprising case: You all know the effects of arsenious acid, so much used as a poison, especially in former times, when the method of ascertaining its presence in a dead body was unknown. Arsenic, so violent when in a free state, loses all activity when it is made to enter into a combination called cacodyle. Cacodylic acid, which contains 54 per cent. of arsenic, can be introduced in enormous quantities in the economy, without any ill effect. You see that here we have evident demonstration that owing to a peculiar mode of combination, properties pertaining to elementary matter may be concealed, in the same way that a while ago I showed you that new modes of arrangement give rise to properties which did not previously exist.

Elementary composition is therefore absolutely insufficient to explain the properties of medicaments and their diversity of action. Shall we, then, take into account chemical constitution, and shall we attach to that structure all the importance we have been obliged to withdraw from elementary constitution?

This is a point in the history of therapeutics on which I am obliged to dwell, because it has been made conspicuous in a certain number of recent French and foreign works. As early as 1841, Black, an English chemist, said that molecular structure alone is of importance in medicaments. He endeavored to demonstrate that substances might differ greatly in their constitution, but owing to the fact that they were isomorphous, they exercised the same therapeutic action. He had evidenlty forgotten that substances which crystallize in the same form are already substances of nearly analogous elements. For example, let us take the hyphosphate of lime and the tri-arseniate, which are isomorphous. I have shown you that this last enters into the bones and takes the place of the hyphosphate. But to what is this due? Not because they are isomorphous, but because their constituents are analogous. Therefore, it is not isomorphism which causes identity of physiological action; this last is due to fundamental analogies between the elements of bodies that are isomorphous. Consequently, you see that it is impossible to rely solely upon

structure, for isomorphism indicates molecular structure in the same way as the several fragments of a column are expressive of the column in its entirety.

There are structures which, although similar, have considerable difference in their physiological and therapeutic action, while again, there are dissimilar structures with considerable resemblance as regards these same actions. It is, therefore, impossible to give that importance to Black's opinion which he supposed it deserved.

But there are experiments of a most interesting kind, which bear upon capital points in therapeutics, and which will show you how secondary is structure in a certain number of cases.

These experiments are those made almost simultaneously by Crum-Brown and Thomas Fraser, in England, and in France by Jolyet and André Cahours. They establish this: That in a molecule of an alkaloid, (let us take quinine, strychnine or morphine,) one or more atoms of hydrogen may be replaced by one or more atoms of ethyl or methyl, without changing the structure of that molecule. If Black's opinion was well founded, there should not be any noteworthy change in the physiological action of that molecule, which remains what it was, as regards its structure. Well, not only is the action no longer identical, but it is at times the reverse of what primitively existed.

One of the principal alkaloids upon which the French and English experimentalists, almost at the same time, (the first publication was, however, by Fraser,) made investigations, was strychnine. They substituted molecules of ethyl for the hydrogen of this alkaloid, and in that way obtained new alkaloids, among which was *ethylostrychnium*. They experimented upon them, and observed the widest differences between them and the original alkaloid; differences which, at times, amounted to the most absolute antagonism.

But what is of especial interest to us is what takes place with regard to strychnine. In experimenting with ethylostrychnium it was found that in place of having an agent producing convulsions and tetanus, we had, on the contrary, a substance which

paralyzed the motor system, by acting particularly upon the peripheral extremities of the motor nerves. Now, remember the beautiful experiments made by Cl. Bernard upon curara, and you will see that it has exactly the same manner of acting. This is the more remarkable because travelers had informed us that curara was supplied by lianes belonging to the genus *Strychnos.* The principal strychnias employed are the *strychnos toxifera, colubrina* and *castellana.*

According to the report of travelers, the natives boil these lianes in a kettle, and from the residuum, at the end of more or less time, they obtain the curara. But how is it that by this operation a *strychnos,* which is an agent producing tetanus, should be converted into a paralyzing substance?

Now that we know that so slight a modification in the composition of strychnine suffices to change it from an agent producing tetanus into one producing paralysis, we understand how it is possible that the alkaloids of the *strychnos* can be so modified in the operation to which they are submitted by the natives, as to be converted into *ethylostrychnium.* This idea of similitude between curara and strychnine, which I advanced long ago, has been adopted by Fraser himself.

I must add, however, that the analyses which have been made of curara do not aid in demonstrating any identity between ethylostrychnium and the active principle in curara. But the differences are so very fugitive, that unless great delicacy of manipulation is observed they are not noticed.

There are also analogous facts for morphine. Morphine is one of the most powerful of hypnotics. All that is necessary is to take from it a molecule of water to convert it, without change of structure, into apomorphine, which is an emetic substance. This change amounts to so little, that it has but to be placed under favorable conditions to be again transformed into morphine. Clearly it cannot be said that properties are attached to molecular structure.

I add, without delay, because it is an interesting point, that *sanguinarine,* which is the alkaloid of a papaveraceæ, contains

an active substance, which possesses precisely the properties of apomorphine, as if, in the papaveraceæ family, there was a particular structure for active principles, and that this structure gave rise to morphine in the poppy, and in the neighboring plants to an active substance which reminds us of morphine when stripped of a molecule of water.

Upon the whole, when we recapitulate the causes for modifications of a chemical nature, which exert a more or less considerable influence upon medicaments, as regards their action, we see that particular weight should be given to elementary constitution and to molecular grouping. Some weight should also be given to structure, which usually takes place around the nitrogen when organic compounds are concerned, as, also, to the state of dynamization of the compounds in question.

I now proceed to the study of the means, by the aid of which medicaments are able to diffuse their action throughout the whole economy, while their application has only taken place upon a circumscribed point. What are the means of diffusion for medicamental actions? These means are various, and I shall now review them in succession.

Let us first find the conveyance of the medicament, then the propagation of the effects which the medicament has produced upon the point with which it has been in contact. The conveyance of active principles is accomplished by quite a variety of mechanisms. For example, when you introduce into the corner of the eye a drop of a concentrated solution of atropine, you soon notice that the whole of the eye is wet, and that in consequence there is a dissemination which enables the medicament to be absorbed by a more extended surface. In the same way, when you introduce a medicament into the alimentary duct, it is at first received in the mouth—the vestibule of the digestive organs. If it is not very soluble, it may go through the whole extent of the digestive duct. Let us suppose that this substance is introduced into the cellular tissue. Here there is a sort of imbibition by capillarity. You notice a diffusion of the liquid taking place under the skin. If you introduce the substance under the hide of an

animal that can be killed, you observe that at a given moment the substance has spread itself in a circle of greater or less extent, according to its diffusiveness, and the conditions of the tissue in which it happens to be. These phenomena are produced by means of what is called capillarity, and also by means of osmosis, endosmosis and exosmosis.

You see the histological elements of the different tissues loading themselves with active principles. When these active principles disseminate themselves, in the same way as in the sub-cutaneous celluar tissue, they meet with capillary vessels of all kinds; veins, lymphatics, arteries. They are then absorbed, and when once absorbed they circulate through the whole organism and lodge in different organs, according to their affinity. Here there is a mode of diffusion for active substance, first by imbibition, later by circulation.

We shall now see how actions which have been exercised on a given point are propagated, when the active substance is not disseminated in the economy. These actions are propagated by virtue of what the ancients called sympathy. But, wishing to account for these phenomena, we have gone further, and it is here that we have to call in the law of reflex actions. For example, you apply a sinapism. Its active substance is not absorbed, yet, for all that, if it has been applied to a patient in a swoon, you will see the patient reviving and opening his eyes. By what process has this phenomenon been produced? Through the medium of a reflex act; first pain, then an impression upon a sentient nerve on the cutaneous periphery; conveyance of this impression to a nerve centre and excitement of the latter; then return of the excitement towards the heart. When you introduce into the stomach of a patient in a fainting-fit a spirituous liquid, before it is absorbed the patient is revived. It is by reflex action that the propagation and generalization of the local effect produced upon the gastric membrane has been made.

Another means is what Hunter called the sympathy of *continuity* and of *contiguity*. That is, sympathy between two portions of the same organ, or else between two organs which are in

contact one with the other. Nothing is easier than to understand this class of sympathetic phenomena, when, for example, we study the progress of inflammation. You know to what extent inflammation has been discussed; some interposing the lymphatics, and others resting their case upon venous continuity, and others, finally, upon the nerves. None of these opinions explain the facts in the case. How are we to understand these circular inflammations brought on by any cause whatever? How are we to understand this regularity of circular development, when the point at issue is the parenchyma of a spherical surface, with the aid of vessels following a determined direction? I will say as much with regard to the nervous system. When you have applied an irritating substance upon a peripherical region, the irritation spreads from place to place, from element to element, as if there existed in that region a sort of equilibrium of tension or of force between the different elementary parts of the tissues, which is the reason that when you have excited irritation in the one, the other takes part in it. In this way you can understand how it is possible for irritation to extend in a circular form, and how, losing its intensity in the ratio of the square of the radius, there comes a point where it is no longer perceptible. Here, then, is a mechanism by the aid of which you are able to account for certain physiological actions.

This mechanism is not very rare. It is rather difficult to demonstrate, but we are conscious that it exists. Here, for example, is a case: You make use of poultices for a deep-seated pain in the stomach. You must have a reason to give, in order to explain their action. Poultices, as many other topics, are means of occlusion, capable of sheltering a portion of the periphery from the influence of exterior agents, and they act, not only upon the very spot on which they are applied, but also over a more or less remote extent. It is enough, in fact, to have placed the peripehery under particular conditions as regards the state of tension, to secure that from place to place a like state will reach the parts which are more or less in connection with the point in the periphery upon which you are acting.

Trousseau often said that it was possible to cure extended affections, inaccessible to our local or topical agents, by only modifying a portion of the diseased part. He had no hesitation in saying that when we had to deal with inflammations of the post-pharyngeal tract, which extends to near the œsophagus, with granulations, and with tubercular ulcerations, it was enough to modify a portion of the surface, that is accessible to our eyes, in order also to modify the rest. This might be expressed in this wise: As there is a contagion of disease, so is there a contagion in cures. If you soothe a part of a region, by that very act you soothe the whole of that region.

As the chemical medicaments can only exercise their action by contact, many actions cannot be exercised, except through the diffusion of active principles in the economy, and not by the agency of the sympathy. It follows that contact should be immedidiate between the acting substance and the organ which is to receive its impression. Absorption is, therefore, a general condition for the modification of organs by the agents which we bring in contact at times with the skin; then, again, with the mucous membranes. What, now, are the conditions for medicamental absorption? The liquid state or possible liquefaction is almost a *sine qua non*. You will observe that I do not say solubility in water. I speak of the liquid state, because there are fatty liquids which are immediately absorbed.

You know that those liquids are directly absorbed by the intestinal villi, at the summit of which there are sorts of funnels, formed by wide epithelial cells. In these cells the fatty matters are received, and they go through them to pass into the underlying vessels, in the same way that you effect the filtration of a fatty substance through a filter, provided you have first moistened the latter with oil. I was, therefore, right in saying that it was liquidity and not solubility which was necessary.

Substances soluble in water are those most readily absorbed, but there are a great many which seem insoluble in it, and which yet are absorbed. In fact, there exists in the primæ viæ a certain number of chemical principles which favor the solution of differ-

ent substances destined to become medicaments Thus, in the stomach, bases meet with acids; acid substances find bases. In the second portion of the digestive duct there are salts, such as chloride of sodium, and it is here that Mialhe's beautiful experiment finds a place. There are, above all, fatty substances, which favor the solution of sulphur, of phosphorus, and even of arsenic. Finally, there is also albumen and albuminoidal matters. One can form no idea of the power these last substances have over others which are insoluble, even when they have been freed from chlodide of sodium, from the mere fact that an agent meets with mucus, or with albumen, dissolution sets in, within a more or less short space of time, and this is one of the best methods for favoring solution.

CHAPTER V

Avenues for the Introduction of Medicaments.

SOLVENT ACTION OF ALBUMEN.
The part of Gravity in Absorption—Gingival deposits, tattooing

AVENUES FOR INTRODUCING MEDICAMENTS: *Digestive Tract*—The mouth, infantile syphilis, neuralgia of the fifth pair.
Stomach—Inconveniences of this method.—Decomposition of medicaments in the stomach.

GENTLEMEN:

At the close of the last lesson I spoke of albumen; there is, indeed, a circumstance which has been but recently known, and which plays a most important part: it is the solubility of a great number of substances insoluble in water, in albuminoidal products, such as the albumen, properly so called, and the mucus, which may be met with in the primæ viæ. Wherever albuminoidal substances are found, they are great solvents of matters which, by themselves, are absolutely insoluble. Thus metallic mercury may be dissolved in albumen and in analogous substances. You see that the number of solvents which can facilitate absorption is very considerable, and, above all, these solvents may be everywhere found.

But is it only dissolved substances that can penetrate into the circulation and be carried along by it? No; there are solid substances which may be and which are absorbed in a solid state. This is, I admit, more a matter of curiosity, but it nevertheless deserves some consideration, because there are interesting particularities attached to it.

Rabbits have been fed by mixing a great deal of charcoal in their food; and after a certain time it was observed that charcoal

was present in their pre-vertebral and mesenteric ganglions. These experiments are easier when carried out upon that unfortunate frog, the habitual victim of our experiments. Thus, when it is fed upon starch, to which particles of charcoal have been added, the charcoal is shown almost all through it; it finally becomes pigmented throughout almost all its tissues.

These experiments have been regularly made by Osterlein. At a later date they have been continued by Eberhard, by Kölliker, whose name is well known to you, by Meyer, by Donders, and finally by Mensonidés. They all obtained the same results. It is therefore evident that solid substances may penetrate into the vessels.

At first sight it is difficult to understand this passage, but after a little reflection it is clear that there is nothing very surprising about it. Look at the gingival line which shows itself among workmen exposed to the emanations from lead. The lead particles reach gums which are more or less soft, which among workmen are often bleeding, they are deposited there, penetrate from their own weight, and are finally enveloped by the tissues as the gradual organic renovation progresses. This process unfolds to us the way by which solid particles may penetrate into the vessels. The particles are deposited upon a given spot, they are finally enveloped by the tissues and can then circulate to such an extent that when the operation of tattooing is practiced the colored substances, either red or blue, show themselves in the axillary ganglions; while the tattooing was practiced upon the forearm, the only way they could reach there was through the circulation. But this is not a practical method of causing medicinal substances to penetrate into the organism, and besides, this might cause emboli in those parts where circulation is more difficult.

In short, without considering fluids other than those which are aqueous, it may be said that the substances which best penetrate by absorption, are those which, in the first place, are soluble in water, or miscible with water.

I have now reached one of the most interesting questions for us: it is that of the *avenues* by which medicaments may be

introduced. A distinction is to be established between the place of application and the avenue of introduction.

Medicaments can be placed almost anywhere, on conditions of having instruments which can penetrate with more or less facility. But we should only call avenues of introduction those which in an intentional or accidental way are open to medicaments.

But we must acknowledge that where we only wish to produce topical effects, we may also produce general effects. Thus it is that when you will treat secondary or more or less advanced syphilitic lesions by mercury applied topically, you must be on your guard against absorption. For if the surface is of sufficient extent, it may happen that you will superinduce stomatitis. Consequently, *place of application* and *avenue of introduction* are two things which are often confounded.

The avenues of introduction of medicaments may be divided into five categories. The mucous membranes are most used for this purpose. They are divided into the digestive duct, the respiratory organs, the uro-genital apparatus, the visual apparatus and the auditory apparatus.

I have placed the digestive duct at the head of the list because it is the most convenient and open to use. We find there the mouth, the stomach, and the rectum.

In the respiratory apparatus we have the nasal fossa, which is a place of absorption of far greater importance than supposed, many cases of poisoning having taken place from collyria, simply because they passed into the nasal fossa by the lacrymal points. We also have the bronchiæ and the alveoli of the lungs. There is at present quite a fashionable method, and a very interesting one, which addresses itself to this way of introduction—it is that of inhalations or inspirations of vapors or liquids in an ethereal form.

With the uro-genital apparatus we have absorption through the ureter, the bladder, and the vagina; with the eye, by the conjunctiva and the cornea; with the ear, by the meatus, the Eustachian tube, and the drum of the tympanum.

Another large surface, equally open for absorption, is the

cutaneous periphery. Several conditions are to be considered, according as absorption is to take place through the unimpaired skin or not. If the skin is unimpaired, we then have to consider a few modifications; either we are satisfied with applying medicaments to its surface, or else, on the contrary, we follow very ancient processes which have been methodized at a later date—one is, that by frictions we succeed in forcing open the pores of the epidermis, and thus bringing the dermis to absorb substances which could not have penetrated otherwise. A second process is absorption by the denuded skin, that is, the endermic or diadermic method. This method enjoyed great populartiy, but at the present day it has nearly gone out of use, having been replaced by the hypodermic method, which consists in the introduction of the substances into the sub-cutaneous cellular tissue. Yet another method is that inaugurated by Lafargue de Saint-Emilion. He introduced the substances into the dermis. It might be called the infancy of that method which we designate by the name of *hypodermic*. This plan has had antecedents, although it appears recent. It was preceded by the plan of creating an artificial cavity, in which medicamental substances were deposited in the cellular tissue. Thus Trousseau made incisions and deposited on a level with the origin of the sciatic, the value of a pea of belladonna or opium, which were his principal agents.

No doubt this already belonged to the hypodermic method, but it was of a most primitive kind, and did not possess the value of that very elegant method founded by Pravaz' practice.

We also have another method which has been so thoroughly modified by one of my former students, Mr. Luton,[1] that we may say it belongs to him. He had the idea of introducing medicinal substances at times in parenchymas, then again in deep-seated regions, as in deep-seated cellular tissue of a limb, in the ganglions and the thyroid gland. This method is called the *method of parenchymatous substitution*. The author employs it,

1. Luton on Sub-cutaneous Injections with Local Effects, Paris, 1875.

especially in producing inflammatory effects, which induce the destruction of parts which were the seat either of an induration or of a chronic inflammation. But also when, by this method, absorbable substances are introduced, they produce diffused and generalized effects, and on that account it deserves a place here.

At times sores and fistulas are used as avenues of introduction. Thus, chloral has been introduced into fistulas, and the pains have been allayed. In the same way, tincture of iodine has been introduced, and not only has a modification of the sores been brought about, but also an absorption of iodine, which is of benefit to those troubled with scrofulous affections. The serous cavities would prove useful, but for this drawback: that they are highly irritable, and thus give rise to phenomena of the greatest gravity, as, for example, when the peritoneum is concerned.

Although medicinal absorption through serous cavities has been observed, it is not a plan that can be recommended. I speak of this because, when iodine has been introduced into an articular serous cavity, phenomena of more or less intense iodism have, at times, been witnessed.

Mention may also be made of the introduction of active substances into the vascular system, in the veins and the arteries. This is what is called *transfusion*. This method already dates two centuries back. It was at first practiced upon animals, then upon man. It was not so much medicamental substances that were introduced as blood—at times, that of animals, then, again, human blood, when it was necessary to revive more or less debilitated patients. This operation dates back to 1665, upon animals, and to 1677 on man.

These are exceptional means, and I say to you in advance that I do not, in the least, approve of the introduction into the veins of substances capable of producing sleep. These are dangerous methods, and they have shown their effects by phenomena of the most serious nature.

The above are the several means of introducing medicaments. I now have to speak to you of the principal one. That

is, of the administration of medicaments through the digestive organs.

I commence by the mouth. It is a part of the digestive duct, which, at first sight, seems to you of but little avail for medicinal purposes. It is a part where the epithelium is very dense, and it is also a thoroughfare. Nevertheless, the mouth is an entrance door which is not to be overlooked. By its agency it is possible to obtain the absorption of medicinal substances, which, by other processes and other ways, would be with difficulty absorbed. For example, through the mouth we can obtain the absorption of liquid and solid substances, which otherwise would be of difficult deglutition. Solid substances are applied to the mouth by the aid of frictions. They are spread on the more or less extended surface of the inner side of the cheeks and under the tongue. The quantity of substance thus deposited, by reason of its nature, is sufficient to act, and in a certain number of cases excellent results are obtained.

Thus, in the event of syphilis among new-born children, it is very difficult to make them take medicine. On an emergency, some of Van Swieten's solution might be mixed with milk, but often children refuse everything else but the breast. In such a case it is an established custom to practice frictions on the interior of the cheeks with proto-iodide of mercury, and the quantity thus absorbed is sufficient to cure the syphilis. Formerly it was permissible to administer to the nurse the medication which was to cure the child, but this cannot be done at the present day with the modifications which our ideas of morality have undergone, unless it be that the nurse is also the mother. We have not the right of treating a hired nurse for a disease which she has not.

There are also circumstances in which generalized effects are not needed, but where localized ones are desirable. For example: In neuralgias of the fifth pair, very often a bit of raw cotton impregnated with ether or chloroform is placed between the dental arch and the cheek. In analogous conditions, Trousseau even used extract of belladonna. As to the stomach, I have no

hesitation in saying that there exist, on the nature of stomachic absorption, illusions, which have been completely destroyed by experiments conducted in due form. Indeed, it is not an absorbing organ, absorption only taking place in it in a slow and difficult manner. You have only to reflect upon the conditions in which it finds itself, either when it is in a state of vacuity or when it is full. In vacuity, the stomach is in a constant state of desquamation, which forms on its internal face a gelatiniform coating, and this goes on increasing in the intervals between meals. If there is a saburral condition, an enormous mass of this substance is found covering the lining membrane, so that a medicinal substance happening to fall into such a stomach, only with great difficulty finds the means of placing itself in contact with the absorbing surface. Alimentary residues are also often found therein. Even among healthy people it is not rare to find these, from four to six hours after a meal. There are also ferments of various kinds; also acids, which, in certain cases, are injurious to medicaments. Finally, the stay of substances in the stomach is, of necessity, a prolonged one, and this sojourn which appears favorable to absorption becomes unfavorable, when there are present ferments, etc. Under these conditions, medicinal substances which have penetrated into the stomach, and which remain there, may become deteriorated. Consequently, possessing a better knowledge of the physiological conditions of the stomach, we are able to understand why it is a questionable avenue for absorption.

I stated that experiments had given prominence to this inferiority of the stomach. One of these, due to Claude Bernard, consists in the introduction into the stomach, after ligature of the pylorus, of a more or less dilute solution of strychnine. So long as the pyloric orifice remains closed there is no tetanus, nor are there convulsions produced by this alkaloid. But if the ligature is slackened, in a few minutes the phenomena of tetanus are induced.

The substances had not been destroyed by the stomach, as could be proved by taking some of the liquid contained in this stomach

and giving it to another animal; this last would experience all the symptoms of convulsing alkaloids.

It is evident that the degree of resistance to absorption will vary according to the nature of the substance presented. Thus there are observations, already rather old, which prove that water is readily absorbed, while there are others which show that substances which are extremely dyalizable, such as yellow prussiate of potassium and iron, are also absorbed with comparative ease; others, among which is curara, are absorbed only with great difficulty, and which, in consequence, should not be entrusted to it.

I could again recall to you here an experiment made by Cl. Bernard. He showed that when the mucous membrane of the stomach was uninjured, curara could be introduced into it without causing any of the accidents to which it gives rise when thrown into the vascular system. When it is introduced into the stomach filled with food, at first sight it would appear that it should mingle with the chymous pulp, and then be brought into contact with the stomachic mucous membrane; but, in the stomach, things do not exactly happen as was imagined a certain number of years ago. It must not be supposed that it is a mere cavity in which a mixture of substances takes place. By feeding rabbits during three days upon grass, then during one day upon carrots, Cl. Bernard demonstrated that these last, recently introduced, formed a sort of cylinder, which occupied the central portion of the chymous pulp.

Under such conditions it is difficult for the substance to come within reach of the mucous membrane in order to be absorbed; it remains united with the alimentary pulp, and it can only be absorbed when these matters dissociate in the lesser intestines.

Thus, as you see, great difficulties are offered to stomachic absorption, either when the stomach is empty or when it is filled with food. When the conditions I have just pointed out to you exist, one can understand how it is that the medicinal substances entrusted to the digestive duct are submitted to such actions, that their effects are enormously reduced and at times almost null.

Think of what must take place in the case I have just mentioned to you, in a substance like digitaline, which is liable to undergo chemical actions of every kind, and which will meet with acids and with oxygen (for we swallow air.) Do not substances like digitaline, which are eminently active when in a free state and not engaged in combinations, lose all their activity when they are consumed?

See what takes place as to phosphorus, a pre-eminently poisonous substance when in a free state. This same phosphorus, when it meets in the stomach with a considerable quantity of air, can be transformed into phosphorous and phosphoric acids, so as to form a sort of intellectual lemonade, as the Germans call it, and this does not give rise to any of the accidents which are produced by the pure metalloid.

Double decompositions also take place in the stomach, and these cause substances which are very active, to produce hardly any effects at all. For it is evident that if you take glyosides—digitaline, for example—and introduce it into a stomach containing ferments capable of transforming those substances into sugar, on the one hand, and some other substance on the other, you will no longer have digitaline. This is the reason why, in a certain number of cases, no results whatever are obtained in a stomach that contains alimentary fragments.

What I have said of the glycosides, I shall likewise say of the intermediary alkaloids between the glycosides and the typical alkaloids. There are, for example, a certain number of nitrogenized alkaloids which, nevertheless, when they are introduced into the economy, behave like the glycosides, that is, they become altered and are decomposed in such a way that in the secretions, particularly in the urine, they are no longer found.

For example, there is in boxwood an alkaloid buxine, which possesses all the qualities of which I spoke a while ago, so much so, that when we come to examine the urine, although the dose may have been increased to two grammes, nothing of it is found. There are others, like esculine, which is derived from the bark of the horse-chestnut tree, and even contain alkaloids, as aco-

nite, which are of such great instability that they become altered from the moment that they meet in the stomach with substances that are somewhat active. This is the reason why aconitine, which can be one of the most violent of poisons, can also show itself almost inert, according to the conditions in which the stomach happens to be.

You see that all those phenomena have considerable importance.

The practical rule to bé deducted from what I have just said, is the following: organic substances must be administered while fasting, especially when they are easily alterable. The recommendation is absolute, when atropine and aconitine are concerned; it is again nearly so in regard to the alkaloids from the poppy, although they are far more stable. But if active substances find a stomach laden with food, they will in great measure be altered. You must even avoid smelling dishes which you relish, avoid smelling the odors from the kitchens, avoid taking broth—all these things are to be shunned, because they are enough to call forth a very active secretion of gastric juice.

We all know that the tempting of a dog by holding a piece of meat to his muzzle, will cause the gastric juice to gush forth, and if at the same time Vichy water is given to him, it will come as a real dew, a perfect rain. Consequently, administer those substances as remote as possible from meals, and away from the presence of food. On the contrary, we can give at meals, or just before eating, those substances which offer greater resistance, such as the alkaloids from cinchona.

Trousseau had observed that some stomachs became rebellious to quinine; it then occurred to him to give it at meal-time. Doubtless in this way it was better tolerated, but there is no doubt that it produced less notable effects, and that considerable quantities of quinine salts were required to obtain results—to obtain the effects of twenty-five or thirty centigrammes, not less than fifty were required. It is, especially desirable when metals are concerned, that the remedies should be administered at the same time with the food.

CHAPTER VI.

Avenues for the Introduction of Medicaments-- [*Continued.*]

The Stomach—continued—Intolerance, trismus, esophageal spasm, cancer; advantage in introducing medicaments through the stomach; histogenetic medicaments, alteratives, iron, arsenic.

Lesser Intestine—The proper methods by which to retain its functions of absorption, after introduction through the stomach; enveloping with fat and with gelatine; advantages of absorption in the intestinal tract.

Larger Intestine—Its advantages, its facilities; medicinal injections; some inconveniences; proper methods for overcoming them; local action; *echos* of sensibility.

GENTLEMEN:

Besides the inconveniences connected with the stomach, inconveniences which I dwelt on at the last lesson, and which are inherent to the method of stomachic ingestion, there are also contingent inconveniences. For example, it is not rare that the gastric mucous membrane, either under the influence of the original disease or under that of repeated doses of an irritating substance, becomes very sensitive. This susceptibility opposes itself to the introduction of medicaments that are in the least irritating. Sulphate of quinine, in particular, can no longer be tolerated, especially when introduced in high doses, as in torrid climates, where two grammes a day are a frequent dose. Under such circumstances, one is placed between two dangers. On the one hand, that of the non-administering of the remedy; on the other, the serious inconveniences which may result from it, as regards the stomachal mucous membrane. There is, besides, the difficulty offered by a certain number of rebellious subjects to the ad-

ministration of medicaments by way of the mouth, as children and women. Even at times an absolute impossibility exists, as with people who are affected with trismus, with esophagœal spasm, and with cancers, either of the mouth, tongue or pharynx.

Notwithstanding all these disadvantages, the avenue of the stomach still remains the best; it is that which must be most used, because it is easy, convenient and natural. To take medicaments by the mouth is doing something analogous to what we do when we introduce food, and the patient, requiring no lessons, leaves to the physician his liberty and preserves his own.

Under our present conditions of life, these are advantages which will cause the oral method always to be most habitually practiced. Besides, it is the only one which is good for a certain number of medicaments. For example, for nourishing ones, for those which have been called analeptics, and which I have called *histogenetics*, that is capable of favoring the genesis of histological elements. Moreover, they are to be administered in such massive doses that it would be impossible to introduce them by the cutaneous way. I have only to mention cod liver oil, of which two, three, and four spoonfuls are taken daily. It is also evident that medicaments, like iron and manganese, could hardly be administered otherwise than by way of the stomach, inasmuch as they require either the liquids of the stomach or those of the digestive duct, in order to be absorbed and properly dissolved.

Besides, I would add, that mixed with the chymous pulp, taking a place already among the peptones, they are half assimilated by the time they reach the circulation.

There are also the alterative medicaments, which are eminently fitted for introduction into the stomachic cavity, and for being absorbed there. I have called these medicaments *metatrophic*, and this is the reason why: You are aware that formerly, apart from those remedies which produce such manifest effects that ordinary sick nurses could verify them, all others were called *alteratives*. Whenever the rudimentary physiology of the period prevented the mode of action of remedies from being understood,

they were classed as alteratives; hence, the number of these was immense. Gradually, physiologists becoming enlightened by observation and experience, the mechanism governing the action of a certain number of remedies was finally understood, so that by degrees alteratives were taken, and placed, some among the nervines, and others with the hypnotics. They were formed into classes, with regard to their therapeutic effects. In the end, after having constantly taken from the list of alteratives, there only remained a small number of substances to which the name might be applied.

On the whole, they are medicaments acting in a slow manner upon the tissues. Among those substances, it is enough for me to mention gold, mercury and iodine. All these act upon nutrition, and this is the reason why I have named them *metatrophics*. They are also substances which, in a certain number of cases, require to be hidden, as it were, in a more or less considerable mass of adjuvants, by which their topical effects are neutralized, they requiring to be assisted in order to become absorbable.

Those substances should likewise be introduced by the stomach. Not only through it, but especially when it is filled with alimentary matter. Thus, for example, iron, which acts as a modifier, in the sense I last mentioned, should be taken just before eating. The same is to be done with arsenical preparations, because the topical inconveniences are diminished, and its dissolution is favored.

In such a case, there is but one circumstance which should prevent the ingestion of the modifying medicament along with the food. It is when this substance exercises an injurious influence upon the labor of digestion.

An interesting chapter might be written on the action of medicaments in the interior of the stomach, and the primæ viæ, the modifications to which they are exposed and their influence upon digestion.

I commenced this study upon phosphorus, because I had observed that when giving it at the moment of taking food,

there appeared, among a certain number of patients, troublesome phenomena of gastric dyspepsia, revealed by the indolence of the digestive duct, and often by eructations. I then conceived the idea of seeking for the influence of phosphorous upon peptic fermentation. I therefore caused a fistula to be made in a dog, and I tested the limpid and abundant gastric juice. I brought this high-grade juice in contact with cubes of meat contained in tubes. I also placed some upon other cubes, of equal quality and weight, but which had been dusted over with phosphide of zinc, which at that time was recommended as an energetic antagonist to paralysis. At the end of a certain number of hours, while the cubes which had not received any phosphide of zinc were softened throughout the whole of their brownish semi-transparent mass, the others had undergone no visible alteration whatever. Consequently, as you see, the powdered phosphide of zinc prevented peptic fermentation. Hence, you will understand, that it must also act in the same manner in the stomach. This is a circumstance to which attention should be given, but we are not well acquainted with the number of medicinal substances that hasten or retard digestive labor.

I now come to the lesser intestine, which is the principal avenue of medicinal absorption.

Active organs are always found there, and they give ample evidences of their absorbent propensities, whether the substances be dissolved in a fatty body or in an aqueous liquid. There still remains, however, principles acting the part of ferments—pancreatine, for example, which can, within a certain measure, modify the constitution of substances, and consequently modify their dynamic activity. But, as absorption is effected rapidly, there is also reason to believe that these alterations will not have time to take place.

There would, therefore, be a very great advantage in throwing the medicinal substance directly into the first portion of the intestine. There are, in fact, certain artifices by the aid of which substances introduced through the mouth may be made to reach the lesser intestine, not intact but less altered than they usually are. They are the following:

The medicament may be introduced in combination with fatty matters, and if these fatty matters are but slightly fluid, or if they only become so at an elevated temperature, they pass through the stomach, retaining the principle with which they have been combined.

We may also inclose the substance first in a gelatinous capsule, then cover it with a wax-like coating. In 1868, I recommended this process for the purpose of introducing bile into the digestive duct of patients who have not enough, and in whom it seems to be an indispensable element in accomplishing digestive labor, or in cases where it was believed that bile could also be a useful agent in a certain number of nervous affections. If you have an object in causing bile to reach the interior of the intestine, it must be encapsuled and coated with some waxy matter, so that it will not disintegrate until it is in contact with the pancreatic juice. This advice has been followed by Mr. Mourrut, who prepares a very useful and much better pancreatine than a number of others which, in part, come to us from beyond the Rhine, and which are absolutely inert.

There is also another process that has been used quite unwittingly, but which nevertheless gives good results.

When you introduce into the stomachic cavity an organized organic product, such as powdered cinchona or colocynth, you, in reality, introduce cells or fibres which contain the active principle, and which only give it up by degrees, as it gradually wends its way in the digestive duct. Under these conditions a great portion of the active substance escapes stomachic dissolution and is only absorbed by the intestine itself.

The introduction by these processes of powdered colocynth, of drastics, like aloes, castor bean, jalap and gamboge, has built up the reputation of a large number of pills. I will not betray the secret, since certain manufacturers make a living by it, but I will tell you that certain pills owe their superiority solely to an envelope which enables them to enter the intestine without alteration. It may be said that the cells of the cellular tissue of colocynth travel the whole length of the intestine, and

only discharge themselves to advantage upon contact with extended mucous surfaces. There results this double advantage—that no action takes place in the upper part of the digestive duct, no revolt of the stomach is produced, and the action is continued during a much longer time.

I now have to speak of the rectum and of the colon. Physiology indicates, in advance, that the rectum and the S of the iliac are excellent tracts for absorption.

How are the fæces modified in these last-mentioned portions of the digestive duct? This modification consists in the draining of the matters. Throughout the whole length of the lesser intestine they remain, so to say, fluid, hardly grumous or pasty; they only become solid in the larger intestine, and their desiccation is completed in the iliac S of the colon, which lengthens the passage. It is consequently a surface constantly open for absorption.

What physiology indicates has been verified by the experience of centuries, and by more recent experimentation. We know of old, the value of clysters and of suppositories. More recently it has been noticed that alimentary substances can be introduced in this way, and can, to a certain measure, take the place of such substances introduced through the upper passages. Nitrogenized substances that are soluble, may thus be used, and even albumen, and especially substances that are more modified and approach nearer to selections from the animal kingdom. There are experiments which prove that by the aid of broth or of wine, it is possible to sustain the strength of subjects who have almost reached the stage of collapse. We often have occasion to use these methods in cases of œsophageal spasms, of trismus, of cancer of the tongue, and in incurable vomitings. There exist numerous observations on the subject by Bouisson, Aran Béhieve, and others.

This is not all. It may be said that, in a certain number of cases, this method is superior to all others. Dupuytren, Chomel, Orfila and Bouchardat have established that for a certain number of remedies, absorption by way of the rectum is preferable

to absorption through the stomach. Of course, it is on condition that the remedy does not require acids in order to be dissolved. For example, a solution of opium, of extract of belladonna, or of strychnine, is more readily absorbed through the rectum and the iliac S, than by the stomach and the lesser intestine, because when substances are retained so long in the stomach, and their absorption prevented for such a length of time, when they do reach the lesser intestine they are often therapeutically and chemically changed.

One cause of fermentation, however, exists: it is the presence of the epithelium, which acts the part of a ferment, as I have endeavored to prove that it did for urine. Urine, in its normal condition in the bladder, only ferments where living elements, at the moment they are detached, fall into the urinary reservoir, where they continue their functional action and act the same part as the histological elements which we call spores of mucedines—that is, veritable ferments.

There has been, however, one discordant voice amid the concert of praise given in favor of the rectal method: it is the voice of my venerated colleague, Briquet, to whom we are indebted for an important monograph on cinchona. He says that quinine given in an injection is not so rapidly absorbed as by the stomach; the difference, however, is not enormous, for, at the expiration of half an hour, it shows itself in the urine.

This fact is explained by a circumstance of a chemical nature. Sulphate of quinine is only slightly soluble by itself. To render it more so, acids have to be added to it, either eau de rabel or else nitric acid. When a solution of bi-sulphate of quinine is introduced into the rectum, it meets there a certain quantity of mucus, which at times is considerable. (All mucus is alkaline, notwithstanding what may have been said to the contrary; if it is acid, it is because fermentation has taken place.) This mucus, which is alkaline, neutralizes a portion of the acid, by the aid of which the sulphate of quinine is held in solution. Hence, absorption takes place more slowly, but it is only necessary to introduce a greater proportion of acid to hasten it, care being taken to pro-

tect the mucous membrane with some mucilaginous substance, like a decoction of marsh-mallow root.

In conclusion, as you see, the rectal plan offers real advantages. There are also some drawbacks. These are of several kinds. Some are purely of a moral order. Among the French you will meet with persons who entertain serious prejudices against this mode of introduction. You must endeavor to overcome them. There is also this other drawback, that we cannot gain full command over the smooth fibres, so that when we introduce into the rectum an irritating substance, capable of exciting the contraction of the muscular membrane of the intestine, the substance is evacuated almost as soon as it is introduced. This is a serious drawback. I will tell you presently how it may be obviated.

There are, moreover, difficulties resulting from certain lesions of the orifice, from hemorrhoidal tumors, from contractions of various kinds, from inflammations, and from fissures, which are, as you know, eminently painful. We have also to contend against the absence of substances in the rectum capable of dissolving the medicaments when once introduced. We find there neither acids nor neutral salts, nor certain ferments, circumstances which are less favorable than are presented in the upper portions of the digestive duct. Add to this, that purgatives which are active when given by the stomach, show less effect when introduced by the rectum.

Aran has pointed out that twelve grammes of scammony resin or of jalap, produce almost no results. But if it be dissolved in a certain quantity of alcohol, and kept in suspension by the aid of the yolk of an egg, it will produce purgative effects. Consequently, this is a slight inferiority, to which I shall attach no importance. There are ways of obviating all these little inconveniences. For example, there is often a large quantity of mucus at the termination of the intestine. When you desire to introduce an important medicament, you must begin by clearing, by the aid of a copious injection, all that portion which is accessible. Another danger is, that a revolt is possible, and that the

rectum may exonerate itself after the remedy is introduced. In that case, you endeavor to render it tolerant, by means of a slightly opiated injection. Or you introduce the least possible amount of vehicle, with the greatest possible quantity of energetic principle. In an extreme case you might introduce extract of belladonna into the rectum, by the aid of the fingers, and after a certain time it would be in condition to retain the medical agent proposed.

If these are inconveniences against which we can guard, there are also positive advantages. One is rapidity of absorption, as demonstrated by Demarquay's experiments. He made a great number of tests to show the differences in the absorbing capacities of the mucous membranes. He obtained his results by the use of iodide of potassium. This salt is highly dialytic, and is absorbed with the greatest facility, even by the stomach. It is, besides, one of the easiest drugs to detect, easier than you perhaps believe. When it is desirable to ascertain the presence of iodine, in a combined state, in a liquid such as urine, we usually go to the trouble of having our druggist prepare a re-agent, and we take endless precautions. All this is useless. It is much more simple to immerse in the test-glass a sheet of paper, folded several times, and then pour a few drops of nitric acid on it. The paper assumes a blue color, the same as starch does. Consequently, these two qualities, great facility for being absorbed, and remarkable ease of detection, recommend iodide of potassium to the attention of experimenters. By its aid Demarquay demonstrated the greater rapidity of absorption by the rectum than by the stomach. Pirogoff and other surgeons have brought on anæsthesia by introducing chloroform by the rectum.

Other circumstances may be mentioned in favor of this avenue. There are substances, disagreeable to the taste and smell, which can be introduced, and their use will spare the patient a certain amount of annoyance.

There are also circumstances in which the stomach declines to receive medicaments of great energy. All physicians from tropical climates who have prescribed sulphate of quinine in

large doses will tell you how embarrassed they have been, when the stomach was in a state of revolt, in regard to continuing a treatment rendered necessary by the disease. In such case we can always procure the absorption of substances by the rectum, except, indeed, when we have to deal with dysenteries.

I must add that when you have to deal with painful diseases of the organs contained in the pelvis, the uterus—ovaries, prostate gland, seminal vesicles and bladder—it is through the rectum that you should act. The reason for it is this: with the same dose of medicinal substance you thus produce a much greater effect upon the intra-pelvic organs, than through the stomach. The reason is plain. When I come to speak of the endermic method, I will show you that preference is to be given to the region nearest the seat of the disease. It is the same with the intra-pelvic organs; when you introduce opium or extract of belladonna into the rectum, you, of course, invoke the aid of absorption, through the whole circulation, but you likewise act from proximate to proximate, by virtue of that sympathy of continuity and contiguity upon which I have already dwelt.

You also act by way of nervous sympathy. That sympathy consists in this: the existence of nervous connection between two neighboring organs being granted, if you place one in a particular condition, the other will imperceptibly be brought to a like state. This sympathy acts in two ways: one, which is known to you, is the response that is obtained from a deep-seated organ to a medicinal application at the periphery; the other is but little known, but I have already called your attention to it.

There are, as yet, unknown paths in anatomy and physiology, but clinical observers have noted them. I once called attention to them in the "Société de Biologie."

You will observe that when you have a pain and you cause friction at the point at which you feel it, you will experience a secondary painful sensation at a distant, but always at the same point; if the seat of the pain changes, that of this secondary pain will also change. You will note that there is a constant order in which these phenomena, which I call *echoes of sensibility*,

are evolved, and that they invariably manifest themselves at a point above that of the primitive pain. If the excitation takes place at the thigh, the painful point is at the abdomen; if at the base of the breast, then the echo will be in a region which is about that of the internal musculo-cutaneous nerve. No doubt what we here notice, where the sensory nerves are concerned, is also produced in that division of the nervous system belonging to organic life.

Finally, there are circumstances in which administration by the rectum is the only plan possible.

As long as I live, I shall never forget the following circumstance: Some years ago, there arrived in Paris a professor from Philadelphia, who consulted a certain number of physicians, myself included. Among other things, I prescribed for him extract of cinchona in doses of one gramme a day. He did what laymen and even sometimes doctors do—he took at one dose what he guessed was a gramme of extract of cinchona. After a few minutes he experienced unutterable distress, and was seized with convulsive movements. His wife, an intelligent lady, concluded that he had been poisoned by strychnine. She went down to the druggist and inquired what had been given. They discovered that it was extract of opium. The man had taken one gramme of gummy extract of opium before his breakfast. He fell into a state of deep coma, and was seized with incoercible vomiting. When I arrived he had been examined by several good physicians, among others by Messrs. Blondeau and Guérin. His condition was desperate, nothing could rouse him from the coma, and as soon as anything was given him, even a little ice, he threw it up. His pallor was extreme; it was believed he was about dying. I ordered that an injection of one gramme of sulphate of quinine be given him, and, thanks to this antidote, he gradually recovered consciousness. The following day almost all traces of poisoning had disappeared. As you see in this case, that patient owed his life to the possibility of introducing an energetic medicament by the rectum.

CHAPTER VII.

Avenues for the Introduction of Medicaments--[Continued.]

Bladder—Weakness of absorbing faculty; except in pathological cases.
Urethra—The same.
Preputial Mucous Membrane—Some local advantages.
Vaginal Mucous Membrane—The same.
Uterine Mucous Membrane—Dangers of this avenue; uterine injections.
Ocular Apparatus—Collyriums: atropine, daturine, duboisine, eserine, picrotoxin.
Nasal Fossæ and Pharynx.
Eustachian Tube; Tympanic Cavity.
Respiratory Organs—Gases and vapors, turpentine, sulphuretted hydrogen.
Liquid Bodies—Rapidity of their absorption.
Solid Bodies.
Pulverulent Solid Bodies—Their introduction in the respiratory organs.—Professional diseases.
Fumigations.—Inhalations.

GENTLEMEN:

We shall to-day continue the study of the avenues of intoduction, by considering the uro-genital apparatus, beginning with the bladder.

For a long time the bladder was considered to offer an excellent absorbing surface, but precise experiments have demonstrated that this was an opinion which nothing justified. *A priori*, they might have guessed that the bladder was not intended for absorption; indeed, if it absorbed, it would have been like the Danaides' seine, since it would thus have allowed the urine to escape, which incessantly flows into it. Fortunately, the bladder does not absorb, and the experiments of the older

Ségalas in 1824, and those of his son, confirm this proposition. Besides, within the last few years, experiments made with extreme care by a young "interne," of whom science has recently been deprived, Mr. E. Alling, have proved that both in man and in animals the bladder does not absorb.

There is, however, no doubt that in a certain number of cases, reliable observers have had occasion to note the existence of general effects, due to the introduction of medicaments into the bladder. How is this to be explained? Simply enough: in a healthy condition the bladder does not absorb, but an ulcerated bladder becomes a very active medium for absorption; and this is precisely why Demarquay, who experimented on cases in which persons had diseases of the urinary organs, witnessed the most dissimilar facts with regard to absorption.

At times it did not take place; no iodine could be traced; then again, a little would be found at the end of from four to six hours; another time it would appear after thirty-five minutes. These differences are explained by the conditions in which the urinary reservoir happened to be. When absorption took place, it was because there were ulcerations; when it failed, it was because the mucous membrane was healthy, and that there were no excoriations. Consequently, we cannot depend on the bladder as a tract for medicinal absorption. In certain cases you may have results, but it will only be where the genital organs in general are impaired.

The urethra is under the same con ditions: when in a healthy state, it absorbs very little—it is not in tended for this purpose; but when inflamed, it becomes absorptive. Thus it is that in a certain number of cases when bougies coated with belladonna have been introduced, phenomena indicating a certain degree of atropism have been observed—that is, dryness of the throat, thirst, with a more or less perceptible amount of mydriasis. Here there is not a real avenue for abrorption, only an accidental one.

As much may be said of the preputial mucous membrane, and yet there is an advantage in knowing some peculiarities it pos-

sesses. It has been observed that solutions of iodide of potassium deposited between the glans and the mucous membrane have been absorbed rapidly, so that the iodine would appear in the urine, although every precaution had been taken to prevent its penetrating directly into the bladder. This has been noticed by careful observers, and in particular by Demarquay. It may be asked, of what advantage is this knowledge? It is this: whenever it is possible to produce local sedative effects without causing the medicament to act upon the whole economy, you are to give preference to such a measure, because the very active remedies which we make use of in such circumstances, always have some disadvantages. For example, in certain nervous affections, such as neuralgias of the neck of the bladder, if the subject has a long prepuce, so that the sedative substance can be retained, you may find it advantageous to make use of this way in order to obtain an abatement of the general effects.

The vaginal mucous membrane has been considered by some as capable of rapid absorption; others have declared it cannot absorb at all. This discrepancy I explain as I did that about the bladder. In a healthy state, this mucous membrane absorbs but poorly, although perhaps rather better than the cystic mucous membrane; but when it is in a vascular condition, which is not rare in cases of vaginism and in leucorrhœa, where there is at all times a loss of epithelium, and in consequence more or less intense redness and even ulceration, then absorption takes place very well, so well, indeed, that serious accidents have been observed to follow the application of active agents. Thus, for example, Van Swieten's liquor having been introduced, absorption has taken place with such rapidity, that although this is not a means of producing phenomena of stomatitis, cases are on record in which acute mecurial effects were experienced. There are also cases in which a certain degree of atropism and of morphinism have been observed, consequent on the introduction of those substances into the vaginal cavity. Extract of belladonna in the vagina has often given rise to the phenomena I but now spoke of, that is, to a dryness of the throat and to thirst. Cases

have even been mentioned in which it has been possible to introduce chloroform, under the form of vapors, and carbonic acid, and thus to determine more or less notable phenomena of anæsthesia.

The facts about absorption by the genital organs in women—and I might extend it to the surfaces of the labia pudendi—should be remembered, because, while it is true that absorption only takes place with difficulty when they are unimpaired, it is proven that it is easy when they are ulcerated. You know how opinions differ on the subject of medicinal baths; it has been observed that they succeed better with women than with men; it is evident that this difference is to be explained by the difference in the mucous membrane exposed to absorption.

I shall now speak of the neck and the body of the uterus. If you refer to anatomy, you will see that here absorption must be easy, because the mucous membrane is of extreme vascularity; its epithelium is in a constant state of desquamation, and consequently it is in the best conditions for absorption, especially when there is not too large a quantity of mucus secreted. This supposition has been confirmed in a great number of cases, and efforts have been made, not only to account for the reality of medicinal absorption by the uterine mucous membrane, but also for its rapidity. By proceeding in the customary way with iodide of potassium, (the experiments were made by Demarquay,) it has been found that this agent is absorbed with such great rapidity, that it can be traced in the urine from a minute and a half to four minutes, at latest, after application. Nevertheless, I do not advise you to make use of this way of introduction for medicaments. We are, at times, obliged to have recourse to topical applications to the neck; rarely should we venture as far as the uterine cavity, for troublesome accidents are sometimes produced when substances are introduced which are capable of producing irritating effects, and you will presently see that such effects are produced by substances which at first sight seem inoffensive.

When injections have been introduced into the uterine cavity,

it has been noticed in a certain number of cases that they were followed almost instantaneously by vomiting and other symptoms of peritonitis.

No doubt by using precautions, by not forcing the injection too energetically, it is possible to avert accidents, but, after all, one is never certain to avoid all such risks. When you give an intra-uterine injection, and you induce serious accidents, are they necessarily due to the essentially irritating qualities of the substances introduced? No; you may introduce distilled water into the uterine cavity and produce most serious accidents. I have had frequent occasion to recall this observation upon one of Trousseau's patients. This patient had an affection of the peritoneum which communicated with the exterior. Trousseau treated him by mucilaginous injections, such as decoctions of marsh-mallow and of poppy. On one occasion the peritoneum having given signs of some slight irritation, the idea occurred to him to make injections with distilled water. The patient was almost immediately taken with extremely acute peritonitis. This might appear surprising, but it is not so, because irritants are not substances endowed with irritating qualities that are inherent to their nature.

An irritant is any substance that possesses properties greatly differing from those of the substances normally in contact with an organ. Hence, with still greater reason, an excitant is any substance whose qualities greatly differ from those of any organ.

I shall give you an instance: The bladder, when we are warm, is sensitive to cold. You are warm; you rise from bed, and are taken with a desire to urinate. You have been a long while exposed to cold. You approach the fire in winter, and there again you have a desire to urinate. To what is this owing? To a change in the conditions under which the organism has, for a certain time, been placed.

The same happens with the peritoneum. When you pour into the peritoneum a liquid, which, by its mild quality, resembles the peritoneal serosity, the peritoneum will tolerate it. But if

you introduce distilled water, that is, the oxide of that metalloid called hydrogen, intense irritation then takes place. That is what occurs when you put distilled water into the eye. It produces a heating sensation. On the contrary, salt water, which is in every way similar to tears, produces no sensation whatever. I mention this so as to make you understand that you will not be safe against accidents, from the mere fact that you make use only of inoffensive substances in uterine injections. With how much greater reason, then, if you introduce perchloride of iron into the uterus, as has been done in cases of fungous tumors

It is a bad process. It is better to make use, as Mr. Richet does, of cauterization with nitrate of silver, because you are certain not to produce a distension, owing to which some of the liquid substance can penetrate into the interior of the tubes, and thus give rise to the most violent irritation, and, after a time, to real peritonitis.

A great deal of discussion has been had upon the manner in which these phenomena take place. The thing which I have just explained seems to me the most probable.

In certain cases inflammation of the uterus may be transmitted to the tubes, and from there to the peritoneum.

There is also another mode of action on the part of the uterus, and that is over the sympathetic nervous system. It is a sort of sympathetic reflex action, comparable to that which you occasionally see developing itself, with such vehemence, when you make use of a catheter. If you introduce a probe, when there is no material obstacle in the urethra, but where there is a paralysis of the bladder, you may thereby give rise to an irritation which will manifest itself by an attack of fever having an intermittent type, comparable in every way to paludal fever. It is a sympathetic reaction. And it is by the same course that a case of deep-seated urethritis determines those phenomena that are called blennorrhagic rheumatism. In this rheumatism the influence of the urethral affection upon the sympathetic system is so well demonstrated, that when you test the urine of patients you develop a blue color in it the same as in that of subjects suffering

from abdominal diseases, an unquestionable proof of the reaction of the affection upon the abdominal sympathetic nervous system.

I shall now say a few words upon the ocular apparatus. The cornea and conjunctiva are tracts in which absorption takes place rapidly. I speak of them especially because you will sometimes notice diffused effects from substances placed on the eye. When a mydriatic collyrium is used—for example, atropine—it is nothing very rare to obtain both a dilatation of the pupil on the side upon which the medicament has been applied, and also phenomena of dryness of the throat and thirst, and visual troubles in the healthy eye. In a certain number of cases, subjects have been seen laboring under that fantastic delirium which characterizes atropism when it assumes a rather serious form, thus proving that absorption had taken place, not only by the conjunctiva and the cornea, but also by the lacrymal sac and the nasal fossæ. When you desire to bring on mydriasis, and you make use of a rather strong atropine collyrium, you must be careful, and introduce but a small quantity at a time, and not pour it *larga manu*, as is often done. I would even add that a concentrated solution should not be prescribed. Very often the limit has been overstepped. Thus, there are ophthalmologists who prescribe gr. 0.20 for 20 grammes of water. This is a dose almost four times too strong. With gr. 0.05 you will obtain all the results you require.

The same holds good with reference to daturine, which certain practitioners prefer. The same recommendation may also be made for the new alkaloid, duboisine. It acts like atropine, and although not as yet within the current domain of therapeutics, it will soon be. And likewise for eserine and picrotoxin, which must never be used in too concentrated forms.

The pharynx is also among the number of mucous membranes which can absorb. It has even been taxed with absorptions which really did not belong to it, as with certain phenomena of narcotism among inveterate snuff-takers. It was said that the tobacco which adhered there allowed its active principles to be absorbed, and that accidents might result therefrom. But with snuff-takers the tobacco is swallowed, and it is far more likely that absorption took place in the stomach.

The Eustachian tube and the tympanic cavity are also localities of absorption. Physicians who give their attention to diseases of these organs, have had occasion to witness the phenomena of diffusion which are not infrequent with the substances employed, especially with atropine. But they are not eligible tracts of absorption for medicaments.

I now come to the consideration of the respiratory organs, properly so called, for in speaking of the nasal fossæ and the pharynx, these are but a common vestibule; they are not the respiratory organs. The larynx, the trachea, the bronchia, finally the pulmonary alveoli, these are the real respiratory organs. This tract offers the greatest facility for medicinal absorption, and the number of medicaments thus introduced is constantly increasing, not only because chemistry supplies us with very active volatile substances, but because we now have at our service the atomizing of liquids, which enables us to introduce not only volatile substances but even stable substances, which do not possess the faculty of being brought to a gaseous state.

Let us first speak of gases and vapors. It is enough to be acquainted with the physiology of respiration, in the essential portion of its history, to understand that gases may introduce themselves readily into the respiratory organs, since it is there that the gaseous exchanges between the blood and the atmosphere take place. Experience constantly illustrates this. When, for example, you sleep in a recently painted room, your urine smells of violets. This will take place if you only remain two or three hours in such a room. Not only does absorption take place, but it is very rapid.

This had been long ago observed by Magendie, who showed that what is called "*plomb*"—that is, those terrible and almost always fatal accidents which befall those who descend into cesspools—are due to the introduction of sulphuretted hydrogen into the blood. Cl. Bernard, his pupil, has demonstrated why this intensity of action is so formidable as an effect of sulphuretted hydrogen. He has shown that if sulphuretted hydrogen is nearly harmless when absorbed by the digestive membrane, as

is the case with sulphurous waters, it is because it can be immediately exhaled by the lungs while it is being absorbed. On the contrary, when it enters into combinations with the globules, the most serious accidents take place, because respiration is suddenly suspended, and it cannot be so, without all the vital phenomena being brought to a standstill. Another example of this instantaneousness is in anæsthetics. At times, a few inhalations of chloroform suffice for narcotism to manifest itself.

As to liquids, their absorption is also extremely active. One is surprised at the rapidity with which it takes place, and at the enormous quantities of liquids which can disappear when they are injected into the respiratory organs. Thus, 30 grammes of water have been introduced into a rabbit's lung; 200 into that of a dog. 10 to 15 litres of water have been introduced into a horse's lung without any accident. This water is rapidly absorbed. So great is this readiness, that Mr. Colin, of Alfort, has demonstrated that a constant current can be established; that is, a liquid can be incessantly poured down a horse's træchea into his lungs, and it is finally possible to kill him by the influence of the ulterior modifications which this water determines in the blood and in the tissues, without a trace of the liquid remaining in the lungs when the animal dies.

When solid substances are dissolved in the water which penetrates into the respiratory organs, it is evident they must be absorbed along with it. Such experiments have been made, and the various substances used in them have been detected at the end of a very short time. Cases of poisoning by those active alkaloids whose characteristic phenomena cannot be mistaken, as strychnine or atropine, have likewise been observed. When atropine is introduced into the respiratory organs of an animal, phenomena of atropism immediately take place, with thirst and delirium, for animals have delirium, which is visible for those who know how to understand it. The same with strychnine. In the space of a few minutes we see tetanic phenomena supervene, and the animal may die, if the quantity is sufficient. When substances like iodide of potassium are used, simply to

demonstrate rapidity of circulation, it is found that at the end of three or four minutes this iodide, introduced by way of the bronchi, shows itself in the urine.

If substances are in a solid state, in the form of dust, can they penetrate into the bronchial ramifications? At first sight this seems rather difficult, for if the way lay so widely open, we should be continually exposed to risks, and there would happen many more serious accidents than what we now see.

Nevertheless, this introduction of dusts does take place, and the accidents to which those men who follow dangerous trades are exposed from this circumstance are known too long a time for any doubt to be possible. For example, wool-carders are subject to bronchitis and to phthisis, and when their autopsy is made, fragments of wool inspired by them are found in their lungs. The same happens to the weavers of cotton, dyed with poisonous aniline colors. The particles of the cotton which find their way into the respiratory organs, give rise to accidents which are well known to those persons who give their attention to hygienic questions. The same happens to those who break and dress stones. Bronze moulders are similarly exposed, and in 1854 Tardieu published a remarkable memoir, in which he called attention to serious accidents experienced by bronze smelters who make use of charcoal dust containing silica.[1]

One must remember, however, that these workmen, like others, blame everything upon their profession, and this, at times, seems warranted by the results of clinical observation, when, in point of fact, it is not the case.

I remember a workman who had the appearance of being tuberculous, and who finally died in a state of phthisis, without tubercles, properly so called. He had, in the inferior portion of the lungs, calculi, which appeared to be formed by the dusts he had breathed. I called attention to the fact that they were not heavy, and Mr. Berthelot and I analyzed them. We found that these calculi were not formed by silica, but by earthy phosphates and carbonates. There was, however, one difficulty, to wit, that

[1] Tardieu. Annals of Public Hygiene and of Legal Med., 1854.

earthy phosphates and carbonates are soluble in concentrated acetic acid, but these were not. This was due to the fact that they were coated with a viscid, albuminoid matter, which prevented them from being acted upon. When submitted first to heat, they then dissolved. You see that some reservations are to be made with regard to the frequency of such accidents

Another case is on record which interests us more than these, and which proves the introduction of dusts in the respiratory organs. It is that of an apprentice in pharmacy, who could not pulverize ipecac. without being taken with an attack of asthma. This access of asthma was evidently connected with the introduction of the finely divided ipecac. dust, which forms very light clouds. Such instances illustrate the introduction of dusts into the respiratory organs.

What becomes of these dusts? At times they form calculi, but they may also penetrate into the vessels and reach distant parts. The process is the same for them as for the particles of charcoal which are detained in the ganglions. With this question another is connected, which has created much sensation. It is that of the transmission of tubercle by contagion. Mr. Villemin,[1] the author of this theory, believes that even a veil bought of a second-hand clothes dealer, may render a woman tuberculous. This is a field which we need not enter. I rest satisfied for the present with having pointed out to you the introduction of dusts into the respiratory organs, and I come to the applications that can be made of this fact in therapeutics.

The respiratory organs have been utilized in many ways, to which different names have been given—fumigations, inhalations, inspirations. These organs have been used in the earliest periods of medicine, for even in those days, patients were made to breathe either the vapors of water alone or vapors laden with aromatic principles. They were also made to breathe vapors containing such substances as gum benzoin and frankincense.

[1] J. Villemin. Studies on Tuberculosis.

CHAPTER VIII.

Respiratory Method.—Inhalations.—Fumigations.

Fumigations—Their origin.—Olfactory inhalations. The part which water performs in fumigations.—Humidity of the atmosphere.—Tetanus: emollient inhalations.—Inhalations of mineral waters: sulphurous inhalations.—Production of sulphurous waters.—The sulphurariæ.

Inhalations of Dry Vapors—Camphor, tar, essence of turpentine.—Eucalyptus, datura and belladonna cigarettes.—Nitre-paper cigarettes.—Inhalation of opium.

Inhalations of Carbonic Acid, of nitrogen, of compressed air, of oxygen.

GENTLEMEN:

Scattered among the works of writers, we find evidence that from the most remote antiquity, vapors, and particularly the vapors of water, have been utilized in medicine. Vapor baths are nothing but confined places in which persons are submitted to a high temperature, and made to inhale the vapor of water. Fumigations with aromatic substances date back to the highest antiquity. The custom of burning incense in religious ceremonies has no other origin.

Why the word "fumigation?" It is that which has remained the longest in use; it has only been replaced by anæsthesia. It is because the ancients did not make use of invisible vapors, of gases properly so called, but of water vapors which presented a dense mist, and of dry vapors, which always give out a little smoke. That is the reason why those processes were called fumigations. This word is still applied to a number of methods by which medicinal substances can be introduced into the respiratory organs; but, in general, the name is reserved for the external use of medicinal vapors. At times dry vapors are used in certain aromatic baths. Arsenical fumigations are also employed,

and others of sulphide of mercury. They are intended to act upon the skin. Watery fumigations are used on the pudendum in cases of hemorrhoids liable to become congested, and also upon young girls whose periods do not come on rightly.

We must bestow special attention on those fumigations known by the name of "inhalations." As early as 1819, a physician by the name of Rapou published a lengthy work for the purpose of demonstrating the importance of this method; it has been called *atmidatric*, and also *eispinoic*, that is, respiratory medication. It possesses considerable advantages. You know what importance it has acquired since the anæsthetic method came into use.

I shall at present speak of the inhaling of humid and dry vapors, and to these last I shall join the inhaling of gas.

I will not dwell upon those inhalations that are no more than olfactions. Persons on the point of fainting are made to inhale substances like ammonia or vinegar, which exercise a pungent action upon the Schneiderian membrane. But this is of little importance, as it is not a way by which medicaments can be introduced into the economy. Water vapor has been employed; it is not, as a rule, used unmixed, yet, when patients are plunged into the atmosphere of a vapor bath, they inhale a great deal of water. In a great many circumstances it is the water especially that acts, far more than the substances that are added to it. It is not customary to cause simple water to be inhaled, yet there are circumstances in which you recommend processes that contribute to this inhalation. In warm countries, for example, in inter-tropical regions, where the humidity is such that the hydrometer indicates 80° or 90°, when you attend persons who present considerable derangements of the nervous system, they are breathing watery vapor; but in warm non-tropical regions, as in the south of Europe or of France, there are affections of the nervous system which are evidently increased by the dryness of the air. When I was at the grand hospital in Milan on my own account, having been wounded, I was placed in a ward that overlooked a small lake. The surgeons congratulated me upon

my having been brought there, because in that ward there never was any *tetanus*. So much so, that this observation having been made a long time previous, the surgeons were in the habit of having transported into that ward those whose wounds being in the hands or the limbs were of a nature to induce tetanus. They even took the precaution to place under the beds earthen pans filled with water, which thus supplied more or less abundant vapors. This is a suggestion which may be useful, and which I have had occasion to recommend in the treatment of tetanus.

I come now to the inhalations of water vapors laden with different principles. Herbs possessing different qualities are often added to the water; at times these are emollient herbs, then again, more or less perfumed herbs, like linden; again, the water is laden with substances like belladonna, night-shade or datura. Such inhalations owe their qualities, in the first place, to the water—for I told you that this was their principal virtue—and secondly, to the substances added to the water.

When emollient herbs are used, it is the water chiefly which acts; it is different, however, in the case of linden, of orange leaves, and of aromatic herbs, belonging to the umbelliferous and labiatæ families—they are anti-spasmodics. Still more is this the case when belladonna, datura, or poppy are concerned, since they contain principles capable of being volatilized.

In popular medicine there is often occasion to use inhalations of vapors charged with anodyne agents, and it would be wrong to neglect them. For example, when in presence of tracheobronchitis in the early stages, especially when the mucous surfaces are extremely parched, that is, when exaggerated secretion has not yet taken place, it may be of benefit to have the patient breathe water vapors laden with narcotic principles like those from belladonna. There are many circumstances in which this can also be useful; at the onset of acute bronchitis, nothing is more soothing than such inhalations. They can be made very simply: hot water is poured into a basin over a certain quantity

of aromatic herbs; by throwing a towel over the head a confined atmosphere is obtained in which the patient respires.

Inhalations of watery vapors laden with mineral principles have an importance which is daily increasing as the use of mineral waters is becoming better understood. Sulphurous waters, which disengage sulphuretted hydrogen, are, above all, those which have been used in this manner. The vapors of hydro-arseniated waters might also be inhaled, because arsenical waters are able to disengage arseniated hydrogen. When water remains for a long time in contact with organic substances, a smell is disengaged which recalls alliaceous orders; I am well aware that the smell of garlic exists when arsenic burns, and consequently I must admit that it burns when in contact with the atmosphere. I have been told by many women, whose sense of smell is more delicate than ours, that they had often detected this alliaceous odor in places where arsenical waters had been kept.

But, in general, sulphurous waters are those which are used for inhalations. These inhalations have been in use for centuries, but it is only since the year 1800, in a small bath in Germany, that they were regularly established. Since then, inhaling apartments have been established at many mineral springs.

There is a certain historical and practical interest in having you here remark, that formerly there were a great many mineral waters which disengaged sulphuretted hydrogen, and which are mentioned in old books as sulphurous and hepatic waters, (the name *liver of sulphur* was given to sulphuret of potassium.) At the present day, they are no longer sulphurous. Is it that the geological conditions have changed? Not in the least. This result is due to an interesting circumstance. Before the waters were under control, when they were kept in their natural reservoirs, in which considerable quantities of organic substances existed, these waters became sulphurous. Thus it is that Louêche, which, probably, owed its first reputation to the fact that its waters were sulphurous, now no longer has waters exhaling the least smell of sulphur; and this because they are under control,

have been cleaned out, and in consequence, no longer undergo any change.

What, then, is the alteration giving rise to sulphuretted hydrogen? The explanation is now familiar, and Foutan, who classes sulphurous waters under two categories—*natural sulphurous waters*, and *accidental sulphurous waters*—gives the process by which this sulphuration takes place. When organic substances are brought in contact with sulphates, particularly with sulphate of lime, this last is reduced and changed to sulphide of calcium, with a constant evolution of sulphuretted hydrogen.

Such was the theory, which, however, offered some slight difficulties. The question was asked: How can substances be such powerful reducing agents when they are composed of but water and carbon, and leave behind carbon as a residuum? A novel and curious fact was, last year, introduced to science, completely changing, it was supposed, the physiognomy of this metamorphosis.

Mr. Plauchud, while studying the sulphurous waters of the south of France, conceived the idea of making a microscopic examination of the organized productions living in those waters. He noticed that however carefully he washed the substances which he desired to study, the next day they still exhaled the same sulphurous smell. He washed those substances with distilled water, and then found that the smell had disappeared. It occurred to him there might be something contained in the ordinary waters which brought on this decomposition. He at length came to the conclusion that when those living organized substances were placed in a solution of sulphate of lime, they instantaneously determined the development of sulphuretted hydrogen. In other words, it is a fermentation, of which the ferment is a species of algæ, which is found in all waters which undergo the sulphuretted modification, and which is to be found in the bottles of non-sulphurous mineral waters, when these smell of rotten eggs. Thus, in all cases, when Spa water smells of sulphur it is because it contains the spores of those plants which, having decomposed the sulphates, have given rise to sulphuretted hydro-

gen. Mr. Plauchud has established a new theory on mineral waters, based upon this fact, and, according to him, it is always the presence of these algæ which gives rise to sulphuretted hydrogen.

One objection is to be made to Plauchud's theory. It is that the sulphurous waters in the Pyrenees, well up at a temperature so high that it is incompatible with the development of what is called the sulfuraria; it never exists in extremely hot waters, and yet these, as they well up, have the sulphurous smell. It is therefore impossible, in this case, to attribute the development of this smell to the sulfuraria.

Some years ago, in 1863, I had the opportunity of making a few experiments which I consider very interesting. It was at Cauterets, and at a time when the spring was not yet artificially enclosed. I made thermometric and microscopic experiments to establish the relations existing between the vegetable species and the temperature. This was the condition of things at the time: At the moment of emergence, as the water flowed from a canal two kilometres in length, it had lost two or three degrees of its temperature; it did not register over + 50, and there was no trace of sulfuraria; a little lower down its course there lived different organisms; still further down, when the temperature had fallen to + 40° or + 42° Cent., the sulfuraria appeared. It was so evidently this temperature that was indispensable to the development of that botanical species known as *leptomitus sulfuraria*, that at one point near where a brook flowed in, causing a decrease of temperature of several degrees, the sulfuraria showed itself, while one or two metres above, the sulfuraria did not exist; it was necessary that the temperature should fall to + 40°.

It is, therefore, evident that the formation of sulphuretted hydrogen cannot be attributed to the presence of the *leptomitus sulfuraria*, which only makes its appearance at the distance of several metres from the source of the mineral waters. This species is found in all sulphurous waters. It assumes a white appearance when it is incrustated with crystals of sulphur. It

cannot be made to account for the development of sulphuretted hydrogen, since it is as yet unborn, when sulphurous water already exists.

But if all sulphurous waters do not owe their qualities to a peculiar fermentation of sulphates, under the influence of a botanical species, the fact is none the less an interesting one, and it holds true as regards accidental mineral waters.

Sulphuretted waters containing soda, being more stable than the others, are preferable for the stomach; cold sulphuretted waters containing lime are especially good for inhalations, because they liberate more sulphuretted hydrogen. Thus employed, these waters are soothing; they are excellent, when you have to deal with erethism of the respiratory organs, during the progress of chronic bronchial affections. They have also substances held in suspension, which, although not volatile, are carried along as vaporization takes place, especially if there is a disengagement of gas, for in that case a sort of ebullition is produced, which divides up the solid substance and projects its particles into the atmosphere. Thus it has been ascertained by chemical observations that fixed salts of the water used are contained in the atmosphere of the inhalation rooms of mineral water establishments, as at Royat, where the waters possess no other volatile substances but carbonic acid. I add, however, that these salts are found in very minute quantities, and that whenever water becomes finely divided there is a great deal of vapor formed, which contains hardly any solid matter.

I come to inhalations of dry vapors. They are of many kinds. Raspail caused *camphor* to be used under the form of inhalations in tubes—of glass or in a goose-quill. There was a time when every one used them. It may have some value, not that it renders one proof against cholera, as alleged, but it is soothing to the respiratory organs.

Tar is in far more frequent use, and there are many persons upon whom its vapors produce very beneficial effects. A vase filled with tar is placed under the foot of the bed, or the steam of heated tar-water is inhaled, or, again, tarred papers may be

employed. The latter are very handy, and I recommend them. They were invented by a druggist of Gers, who devoted his life to discovering the best tar preparations. He prepares a sort of cigar, which contains the aromatic principles of tar in such proportions that it is only necessary to inhale through it in order to feel one's self impregnated with tar. This is an excellent way of concealing one's necessity for using the remedy, and besides it admits of being used while walking.

Inhalations of more or less analogous principles are well known : of *essence of turpentine*, or of the aromatic principles developed by *pine* or *eucalyptus* branches. These are useful methods from which many patients derive benefit. Of course, these branches must not be in too great abundance. You can understand how this may be objectionable, for I have already told you that all aromatic vapors are anæsthetic, and that all hydro-carbons produce effects which are not identical but analogous to anæsthesia, so much so that the prolonged inhalation of essence of turpentine may give rise to accidents similar to those in a case of poisoning.

There are localities in which these odors are supplied by nature. Thus Arcachon is greatly indebted to its pine forests, which are within easy reach of its visitors, where persons go to inhale the vapors of essence of turpentine.

The smoke derived from the combustion of more or less narcotic plants is also used. You all know *datura* and *belladonna cigarettes* and others. It is a question whether these cigarettes are able to exhale active substances, or if such substances are not, perchance, instantaneously burnt. As regards datura or belladonna cigarettes, their smoke does contain alkaloids capable of acting, because their alkaloids are volatile. I admit that a portion must be destroyed, but another portion must escape and be volatilized. In fact, enough is volatilized to give rise to tolerably marked phenomena. You are aware that this method is a favorite one in asthma.

In similar cases use may be made of the gaseous products resulting from the combustion of *nitrified paper*. Tinder impreg-

nated with nitre might also be used. Nicolas Presi was the first to introduce it. This method is often successful in cases where the datura cigarettes fail. Hence, it is well to bear it in mind.

But what is it that acts in this case, for it may well be asked what possible effect can result from the burning of nitrate of potash? Is it carbonic acid? Is it nitrous oxide, or is it oxygen which is active? It is probable they each contribute a little, but it is the oxygen and the nitrous oxide which bring about the discontinuance of the attack. A variety of inhalations much more used, especially in certain regions of the East, are those of opium.

A French physician, Dr. Armand, had the idea of making use of this process. He has constructed a sort of cylinder resembling a pipe, the bowl of which is of globular form and made of porous earth. In this bowl extract of opium is burnt, and the smoke is inhaled through the pipe. These inhalations may have their utility under several circumstances, owing to the rapidity with which anæsthetic effects are produced. In cases of intense dyspnœa, I have seen a sudden calm thus brought on. The inhalation of three or four puffs of this smoke, which contains, as Reveil has shown, almost all the alkaloids of opium, and especially a great deal of morphine, has been enough to produce sufficiently marked effects to bring on narcotizing results in the primæ viæ. I mention it to you that you may see that combustion does not destroy the alkaloids, and that even baneful things may serve a useful purpose, when employed in a proper manner.

I may here refer to the use of those more or less modified hydro-carbon vapors, which constitute anæsthetics, properly so called, and with which nitrous oxide is to be joined. There are, also, inhalations of gases, properly so called, such as carbonic acid gas, nitrogen, compressed air and oxygen. There are a great many springs which evolve such an enormous quantity of gas, and are continually bubbling, so much so, that they have the appearance of boiling. They generally owe this peculiarity to a constant escape of carbónic acid (as at Vichy and Vals.) A great number of foreign springs (Kissingen, for example,) are of

this class. They soothe certain cases of erethism of the respiratory organs. But carbonic acid has not answered expectations. It is a bad anæsthetic. Besides, the external applications made with it have not all the value claimed for them. There are springs which appear as if they contained the same gas, but which only contain nitrogen, perhaps under the form of *entozone*. The illusion is such, that a manufacturer realized a heavy loss by believing he had secured carbonic acid, while it was only nitrogen, of which he could make no use. The nitrogen disengaged by certain mineral waters is not useless, and there are patients who derive great benefit from breathing it. When a large quantity of nitrogen is liberated, it reduces the proportion of oxygen in the atmosphere, and consequently, the conditions of erethism which result from a more or less exaggerated combustion are benefited.

CHAPTER IX.

Aërotherapathy--Atomization of Liquids.

Compressed Air—Its effect; asthma.
Rarified Air—Anæmia at high altitudes.
Inhalations of Oxygen—Accumulation of oxygen in the blood.
Ozone.
On the Atomization of Liquids—Experiments.

GENTLEMEN:

I shall to-day address you on the subject of *air*, and the different modifications it can be made to undergo. It seems, at first sight, that air cannot enter into account among the substances we inhale. But by modifying *pressure*—increasing or decreasing it—it is possible to modify the action of the air in various directions. For example: Air under considerable pressures has often produced excellent results, in a certain number of affections, such as asthma. These results are obtained when the patient is made to breathe air condensed by one or two atmospheres, as that supplied by the ordinary apparatus.

The question arises to what are these favorable results due? Is it to the condensation of oxygen or is it the mechanical action of pressure, so to say, forcing open the passages, through the membranes of the respiratory apparatus, the pulmonary vesicles and the capillary vessels?

It is probable that these two circumstances have each an influence, but an influence which seems to be unequal. The tendency is more and more towards giving the preponderance to the pressure, and the interesting experiments made by Mr. Paul Bert demonstrate, in a telling manner, the influence of high pressures,

either to modify respiration and the nervous system, or to produce more or less dangerous effects, comparable to those of lightning stroke. In these cases it is not the composition of the air, but the pressure exercised by it which produces the effects we witness. It is extremely probable, that even in air compressed under one or two atmospheres, it is mainly pressure which causes the respiratory modifications. In the absence of a rigorous demonstration, I quote an analogy: In the establishments in the streets de Malesherbes and Châteaudun, where baths of compressed air are given, you may witness real cures of asthmatic attacks. This disease does not yield to oxygen; it is not its greater or less proportion which can dispel an attack of asthma, for asthmatics do not require an increase of oxygen, and, as I often say, they are only well when in a second-hand atmosphere. Hence, there are no asthmatics in Paris. Those from the provinces are in a state of beatitude when they arrive there, and are distressed when they again breath the country air, especially the air on the sea shore, that of uplands, and that from the neighborhood of extensive forests. This is so true, that it is only necessary to have such persons return to the interior of Paris in order to prevent the recurrence of their attacks. Such being the case, it is not the greater quantity of oxygen in baths of compressed air which can be the cause of relief. It is more likely that the attacks yield to the pressure itself.

I shall only say a word on the subject of rarified air. Mr. Jourdanet, a distinguished scientist, who for a long time has resided in the high table-lands of Mexico, has ascribed very great importance to rarified air.[1] He has seen it produce anæmia, and he has advised its use as a means against the tendency to tubercles. Having remarked that although Mexicans have a tendency to become anæmics, they are less liable to be tuberculous, he brought these two facts together, and established a sort of antagonism between anæmia and tuberculosis. His conclusion

[1] Jourdanet, Mexico and Tropical America Climates, Hygiene, Diseases. Paris, 1864. Rarified Air in its Relations to Man in Health and Disease. Paris, 1862.

is, that it cannot fail to be of benefit to those suffering from tubercles to breathe the air on high table-lands.

It is very possible that under the conditions in which the high table-lands of Mexico are, there may be no sufferers from tubercles there. With regard to anæmia, I recall a conversation which I had with a distinguished personage who has lived on the high table-land above Quito, at an altitude of 4200 metres. While there he had to put up with a great many privations, but this did not prevent him from taking daily observations, the results of which he sent to the Paris Academy of Sciences. I questioned him for the purpose of learning if at Antizana and at Quito (an altitude of 2200 metres) there were habitual anæmics. He replied that, on the contrary, the population was in splendid physical condition, and that the inhabitants were very vigorous. You see that there are reservations to be made as to the influence of altitude upon the development of anæmia. Hence it were presumption at present to infer a sort of antagonism between anæmia and tuberculosis.

Inhalations of oxygen have long been in use. At the end of the last century, following Fourcroy's example, they were used against asthma. This malady chiefly presenting difficulty of breathing, seemed to call for either condensed air or pure oxygen, since the purpose was to supply air in excess to the patient. In Laënnec's time, oxygen was tried against asthma, but without success. In other cases where better results were obtained, it is evident they had not to contend against asthma, but against real dyspnœa, or, if you prefer, against asthma symptomatic of a lesion of the heart, or of other affections of the thoracic organs. Oxygen does not suit asthmatics, and, for my part, I have never seen it successfully used against asthma, properly so called.

After the negative results obtained by Laënnec, oxygen inhalations fell into disuse. Afterwards, the experiments made by Regnault and Reiset have again called attention to this gas, and it has once more come into favor. Besides, manufacturers and chemists have supplied apparatus allowing inhalations to be

made at home. As you are aware, at the present day large balloons are constructed of impervious vulcanized rubber, which are capable of containing 10, 20, 30, and 100 litres. These balloons are filled with oxygen obtained as pure as possible, but not entirely so, since it always contains a small quantity of carbonic acid. To the balloon provided with its tube, Mr. Limonsin now adapts a double-necked wash bottle, through which the oxygen passes when it is inhaled, and in which it is divested of its carbonic acid. Now that we have a portable apparatus which holds oxygen gas very safely, and which supplies it in a pure state, we may make use of it in many circumstances, and obtain very good results. It is valuable, for instance, in cases of dyspnœa, symptomatic of a lesion of the heart, and when the patient is in a state of cyanosis and almost pulseless. Often after the patients have breathed a few litres of it, (and, if needs be, they might exhaust one of those flasks) you see them greatly relieved for a time. But what you thus obtain in a very restricted manner, with oxygen inhaled in a difficult way, (the patient having to hold the tube in his mouth,) you would obtain far more readily were it possible to breath free oxygen as one does a current of air.

Once in my life it has been in my power thus to cause the breathing of free oxygen coming in considerable quantities. Thanks to the liberality of the Oxyhydric Gas Company, gasometers such as those which contain portable gas, were placed at my disposal. I thus had under a pressure of one and a half atmospheres, a considerable quantity of nearly pure oxygen containing only a very little carbonic acid. The gasometer being placed in the yard at Beaujon, a long tube bringing the gas into my wards, I could have a patient affected with heart disease seated upon a chair, and the current of oxygen discharged in front of him. Well, persons who were the whole day suffocating, who were in a state of cyanosis, chilled, and with a feeble pulse, would walk away unaided after they had remained a short time in that atmosphere of pure oxygen, and they would remain, at times, five or six hours without suffocating. The suffocation would then

gradually return, and they would fall back into their previous condition. Of course it was not the provision of oxygen they carried away with them which was the cause of this long amelioration; their nervous system had undergone a modification.

I just said they carried away with them a provision of oxygen; here is the proof of it: while under the immediate influence of the gas, there was neither elevation of temperature nor stimulation of the respiratory apparatus, nor any increased rapidity of the pulse, but rather a diminution in its beats and increase of volume. On one occasion, while this kind of sedation of the circulating system was taking place, one of my pupils stopped his breathing, and found he could hold his breath for a considerable time. Each of us then did the same, and we undertook to measure the difference which there was according as oxygen had been inhaled or not. Here are some figures: one of my pupils at that time, Dr. Ayello, who, under ordinary circumstances could only hold his breath from 30 to 35 seconds, after breathing oxygen held it for 90 seconds. Another, Dr. Powell, who could only hold his breath during 45 seconds, held it during 110—a little more and it would have been two minutes. I give you these figures, because the proportion always stood in about the same degree, and each of us always experienced the same effect. I add, that those who could hold their breath the longest time, were those whose blood was less rich, whose blood contained the least number of globules. What does that prove? It proves that inhaled oxygen, oxygen pure and free, circulating like air around the subjects, did not produce any more combustion than air itself. It proves, again, that if this oxygen did not burn any more than air within the same time, that it was nevertheless there in the form of a reserve, and that it enabled the breathing to remain suspended. Another inference from these experiments is, that whatever be the quantity of combustible gas introduced into respiration, this gas will only burn in proportion to the number of the globules of the blood. If there are many, the proportion of inhaled oxygen is sooner exhausted; if there are but few, the action progresses more slowly; it is possible to

hold one's breath for a longer time than in the first case, and without suffering.

These interesting facts have also been observed by Mr. Paul Bert, who calls attention to them and others in every way similar,[1] although ignorant of what I had written on the subject. This adds further testimony in favor of the interpretation I have just given you.

I have a word to say about *ozone*. Both useful and harmful qualities are freely attributed to it. I must say that we have no proof either of its usefulness or of its inocuousness. For my part, from what I have seen in Thénard's laboratory, I am convinced that it is dangerous. People always have as an ideal, the breathing of ozone; and every one believes that if the air of forests is so very healthy, it is due to ozone. I do not place myself in antagonism to sturdy beliefs—rather, I accept them; but I believe that ozone can only render really useful services on condition that it exists in very weak proportions in the air. If it happens to be present in any considerable quantity, it will bring on accidents, real intoxications, characterized by extraordinary intensity and rapidity. I remember on one occasion, at the suggestion of P. Thénard, I took repeated inhalations from a flask which contained pure ozone. I noticed nothing at first, but after a few moments I was seized with vertigo. Both he and his father, after having made the same experiment, experienced similar and most unpleasant effects. Imagine the sensations which would be produced by the odors of flowers in a close room, and this carried to their greatest intensity, and you will form some idea of the effects produced by ozone. If it is ever introduced into therapeutics, many precautions will have to be taken in its exhibition.

I am now through with the subject of inhalations of vapors, or gas. But there would evidently be great advantage in introducing through the respiratory organs non-volatile substances. I do not speak of pulverulent substances, but of those which can be held in suspension by water. Remember the absorptive

[1] P. Bert. Barometric Pressure. Paris, 1878.

power of the respiratory tract, and you will understand what advantages there are in introducing non-volatile substances through it.

The atomizing method seems to supply this want, but the question presents itself: Is it necessary to atomize a liquid in order to introduce into the respiratory organs the fixed principles which it may hold in solution? Do we not know how difficult it is to obtain distilled water; that it often requires three distillations before it is completely pure? Nothing is more difficult than to free it from chloride of sodium. It has been shown that if Vichy water is projected on the surface of a red-hot shovel, and the steam is condensed, it contains sesqui-carbonate of soda, and all the other salts of Vichy water. It has also been observed that on all the surfaces of inhaling halls in all watering places, the soluble, but non-volatile, substances contained in the different waters can be detected. It would, therefore, at first sight, appear that all that was necessary would be to volatilize any kind of water, and that its vapor would contain all the principles it held in solution. This is, in a measure, true, but Thénard has shown that it is when the distilling operation has been badly conducted—when bubbles break on the surface of the liquid, and a certain quantity of water passes over, that then the water in the receiver is found to contain fixed mineral substances; but on the contrary, when the operation is well conducted, fixed substances do not pass over during distillation. This shows you that you cannot depend upon simple volatilization in order to cause solid and fixed principles to penetrate, in any considerable quantities, into the respiratory organs.

This desideratum of therapeutics is sought to be obtained by the atomizing process invented by Sales Girons, [1] and for the application of which the director of the mineral waters at Pierrefonds has had an instrument constructed like a pump-barrel,

[1] Sales Girons. Physiological Theory of the Penetration of Dusts into the Respiratory Organs. (*Bull. de l'Acad. de Méd.*, Dec. 10th, 1861.) New Pulverizer of Liquids. (*Bull. de l'Acad. de Méd.*, Feb. 7th, 1865, tome XXX., p. 367.)

throwing a jet which forms a more or less fine spray. These apparatuses have been greatly modified, as regards the motive power and the various mechanical parts, and such improvements have given rise to remarkable modifications in the qualities of the liquid obtained. At first, visible and tangible droplets were ejected. By holding one's hand in front of the apparatus, one could feel a manifest percussion, and brilliant drops were seen, which, when struck by the rays of the sun, gave the colors of the spectrum. Gradually as the apparatus was improved, it has at last been brought to create a kind of mist or haze—a sort of cloud—which reminds one of what may be seen, before sunrise, over swampy regions. That is exactly what you may observe with the perfected apparatus of the present day. It may be said that they obtain a real nebulosity, or haziness, a sort of vesicular vapor. I insist upon the comparison, not that I believe that the vapors, of which I just now spoke, and which constitute the clouds, are vesicular—they are called vesicular vapors—but I may refer to Mr. Jamin, who, while he does not believe that they are vesicular, nevertheless assimilates the appearance of mists to so-called vesicular vapors. For my part, I represent them to my mind as constituted by minute molecules, of which each is the centre of a particular little system. That is what you see in the case of solid dusts, which, notwithstanding their density, when they are of extreme tenuity, can be carried very far; as, for example, the dust from volcanoes. You know that the fine sands of the Sahara desert cross the Mediterranean sea with such ease that when the simoon blows, the city of Marseilles is covered with a peculiar dust from remote Africa. These dusts, although of very dense bodies, are excessively light, owing to the reason I have just given.

After this condition of haziness and excessive division of water has been obtained, the mist then presents qualities differing from those possessed by the coarse atomizations resulting from the first instruments used. The small visible droplets can only be made to penetrate a short distance into the interior of a glass tube, or they can be seen adhering to the lower segment of the

tube. On the contrary, with a mist, you can see the cloud penetrating a very long tube, winding its way through it and issuing from a minute orifice, at its other end, just as the smoke or gases of combustion would do.

The following experiment, made within the last few years by Sales Girons, is conclusive: He imitated the trachea and the bronchi by means of a long glass tube which bifurcated at a certain height, each branch ending by extremities drawn out over a lamp. He then introduced atomized water, under the form of a mist. This penetrated into the tube, rose within it and issued from the small orifices, in the same way as visible smoke or gas would have done. You readily see that under these conditions there is no reason why air laden with this mist should not convey it along into the depths of the respiratory organs. It is probable, that by placing one's self under analogous condition, the mist would behave in the same manner as a gas. Experiments in support of this were made, before the highly improved apparatus I told you of a while ago had been invented, by Ossian Henry upon rabbits. He made them breathe an atomized solution of ferric sulphate, then would kill the animal, and, laying open the respiratory organs, would bring in contact with the different regions a rod dipped in tannin. Tannin and sulphate of iron form ink, and such ink could be produced in the deepest recesses of the bronchial ramifications. These experiments were repeated by Gratiolet, who verified the same statement. They were made anew by Demarquay,[1] who possessed great ardor for the study of experimental science. He likewise made use of ferric chloride and of tannin. He proceeded in the following way: He caused a rabbit to breathe an atomized solution of perchloride of iron, holding it at 20 to 30 metres from the apparatus for a minute, and then allowed it to rest. He would thus replace it several times, and finally kill it. Then with a rod dipped in cyanide of potassium, he verified that the salt of iron had penetrated throughout the lung. He found it even in the pulmonary parenchyma.

[1] Demarquay. On the Penetration of Atomized Liquids into the Respiratory Organs. (*Bull. de l'Academie de Médecine*, Sept. 24th, 1861.)

But here a precaution is to be observed, similar to that recommended by Claude Bernard, when the point was to ascertain the presence of ferro-cyanide of potassium in the stomach. A certain proportion of acid is to be added to the pulmonary parenchyma. For although the ferric chloride is colored, it is not present in sufficient quantities to be easily detected. I add that the lung is so thoroughly reached by atomization, that in some cases more or less serious inflammations are developed.

These experiments upon animals are conclusive. There is one which will appear to you even more so. It was performed in presence of a commission of which Poggiale [1] and Gobley were members. It took place at the Beaujon hospital, upon a nurse, who, after having undergone tracheotomy, had remained subject to considerable dyspnœa. She had paralysis of the vocal ligaments, especially of those on the left side, and on this account her canula had not been taken from her. An apparatus was adjusted so as to close the orifice of the trachea, and she was caused to inhale the atomized vapors of a tannin solution. When the inhalation appeared to have been continued long enough, she was loosened from the apparatus, and then it was found that when the interior of the trachea was touched with ferric chloride, ink was produced. This is an experiment against which nothing can be objected. It is therefore evident that atomized solutions—and I add those especially that are in the form of a mist—penetrate not only into the upper portions of the respiratory organs, but also as far as the pulmonary alveoli. This fact being demonstrated, we can advance to some other inquiries. Does much substance penetrate? Yes; and enough, under certain circumstances, to lead to remarkable results.

But I must here pause to say a few words upon the modifications which the liquids used undergo, either in their chemical composition or in their temperature, because from this knowledge there will result indications for therapeutics.

When the proportion of solid principles originally in solution,

[1] Poggiale. On the Atomizing of Mineral and Medicamental Waters. (*Bull. de l'Academie de Médicine*, Jan., 1862, tome XXVII., pp. 267, 799, 815.)

or in the mineral water is small, these same substances are again found in about the same proportions in the atomized water. If it is the water from Enghien or from Pierrefonds that is tested, there will be present the whole of the sulphide of calcium, the carbonate of lime, the chloride of calcium and the sulphates of lime and of magnesia; in fact, all the fixed salts remain in the water when reduced to a mist, and in the same proportions. That is the result of Ossian Henry's experiments, confirmed by those of Poggiale. An attempt has also been made to ascertain the amount of volatile principles which these same waters lose, and it has been found that in sulphurous waters containing lime, a little more than half of the gas escapes. But this fact is of no importance, from a therapeutic point of view, because sulphuretted hydrogen is always present in abundance.

CHAPTER X.

Atomization of Liquids.

Chemical Alterations of Atomized Mineral Waters.

Physiological Action of Atomized Douches—Percussion, temperature, chemical composition, precautions to be taken; atomizing of sulphate of quinine solutions.

Atomization in Ocular and Uterine Cases.

Aqua-puncture.

GENTLEMEN:

Let us now see what are the chemical alterations which atomized mineral waters may undergo. It has been thought that they must lose oxygen to a high degree. In fact, Ossian Henry has observed, that in atomizing halls, the proportion of oxygen was only represented by 19 $^{5}/_{100}$ per 100, instead of 21. However, this observation has not all the value claimed for it, because it has often been noticed that in halls where there are a great many persons, there is always a lack of oxygen. In order to have the normal proportion of this gas in the air, it is not indispensable that one should be in open country, since we know that in the experiments made at the Sorbonne, 20 $^{84}/_{100}$ of oxygen and 79 $^{16}/_{100}$ of nitrogen have been found, but when one is within an entirely confined place, there is always a diminution in the oxygen. Nevertheless, we should not conclude from this that combustible substances which are in solution in mineral waters, do not undergo de-oxygenation when atomized. This influence exists. It is manifest around sulphurous waters, and especially those degenerated sulphurous waters which contain hyposulphites and large proportions of sulubhates. These waters owe that

change precisely to the combustive influence of oxygen, which changes the sulphur into hyposulphurous and hyposulphuric acids.

I now pass to the physiological effects of these atomized douches. We first distinguish topical effects, themselves connected, on the one hand, with the physical conditions, and on the other with the chemical nature of the substance or the substances held in solution by the water.

The physical effects relate mainly to *percussion* and *temperature.* When one receives a douche, atomized by an imperfect apparatus, in which the orifice is not very fine, and when the pressure is small, the discharge is in the form of drops, which fall to the floor. When this jet is brought in contact with the interior of the throat, and these visible drops come to strike the wall of the pharynx and the entrance to the respiratory organs, all patients complain of a peculiar pricking sensation, which can only be accounted for by the shock from the droplets, which still retain a considerable momentum. At the same time a notable excitation is produced, which may give rise to a sort of dyspnœa, to which one finally becomes accustomed, but which often manifests itself at the start by a slight spasm. A grasping sensation is experienced at the throat, a contraction of all the organs takes place, so much so, that at times it becomes necessary to suspend the action of the water. I must add that when the water is in a nebulous condition, this phenomenon does not take place.

Whatever is the mode of atomizing, however great the tenuity of the drops, the influence of temperature is always present. If one approaches very near to the jet, the initial temperature will make itself be felt with great intensity. Suppose you have very cold water, like the one I spoke of a while ago, say, at $+4°$, or else very hot water, about $+40°$, these will be the temperatures possessed by the atomized jet.

This indicates that it is indispensable to hold the instrument far enough from the entrance of the mouth, that is, at 0^m 10, or at 0^m 15, at the most. It is here that the condition of initial temperature interposes itself. If you place yourself very far from the jet, the water, although cold, may have acquired the

temperature of the surrounding atmosphere; but then, because of the distance, you lose a portion of the water. If, on the contrary, you use water at $+ 40°$, and you place yourself at a distance $0^m 10$ or $0^m 15$, you have water at $+ 30°$ or $+ 32°$, a temperature which is very appropriate. For the best effects, one should feel neither warmth nor chill, since warmth might produce hyperæmia of the surfaces touched; and one should not feel the water cold, otherwise all the effects of a local douche are obtained. In the same way that after an external douche you notice vascular contraction, followed immediately by reactionary phenomena, as redness and elevation of temperature, so you can obtain by means of a cold douche in the interior of the mucous cavities, these first effects of contraction followed by excitation, which may extend beyond the proper limit. You can thus understand why it is indispensable to have water at a definite temperature; it must not be less than $+ 22°$ nor over $+ 32°$.

When these conditions are overlooked, patients suffering from simple chronic diseases, or from those of a tuberculous nature, are exposed to contracting dangerous colds.

There is a third condition to which you must pay particular attention, that is, the chemical nature of the substance held in solution by the water. If, for example, you prescribe atomized douches of astringent solutions, like those of tannin, of iodine, or of nitrate of silver, you must take infinite precautions that those substances, which are very active even when they are diluted, do not penetrate too deeply, otherwise irritations of extreme intensity may be the result. You know that I told you in the last lesson, that when dogs had been made to inhale either tannin or perchloride of iron, these substances had been seen to pass into the pulmonary parenchymæ. Such animals have been attacked with bronchitis and with broncho-pneumonia, and have died from the effects. Under analogous conditions, Trousseau has seen an atomized application of tannin determine the most serious accidents, and a real broncho-pneumonia lay hold on the subject.

What, then, is the process employed so as to avoid such acci-

dents? In the first place, there is a natural and instructive process which may be mentioned. What I said to you a while ago of those sorts of spasms produced by mineral waters, of that defence, so to say, which the respiratory organs offered, I might repeat with still more reason for solutions possessing an irritating chemical action. This defence reveals itself, then, by a real spasm; it is a way of preventing the liquid from penetrating into the depth of the respiratory organs. But, you will tell me, that this is a sorry process, unfavorable, in that the fluid has not even penetrated into the upper portions of the respiratory organs.

The process for obtaining useful results without inconveniences, is the following: when you recommend the atomizing of a solution of tannin, or of nitrate of silver, in cases of chronic ulcerated laryngitis for the purpose of replacing the brush, the douche is to be taken in the ordinary way, but you must caution the patient *not to breathe* while the douche is in action. He stops for a few moments, then applies the douche, so that the atomized water may enter into the most accessible and most elevated portions of the respiratory organs without permitting the dilatation of the thorax, to give it a chance to penetrate into their inner recesses. In other words, douches must be allowed to act by propulsion, and not by inspiration.

It is not necessary to take all these precautions against the topical action of mineral waters, because, although they may present decided activities, those which we daily use have no considerable local effect.

It would be absurd to say that mineral waters cannot serve as medicaments, because they cannot be injurious, for there are waters that are so concentrated and of such intense activity, that they constitute real poisons. I do not speak of the water of Boucheterre, which contains as high as 20 grains of arseniate of soda in each litre, that is, more than ten times as much as those of la Bourboule; but I have reference to a water which they call Riotinto, which contains sulphate of alumina and peroxide of iron in such quantities that it may be said to be a natural

Vilate's solution. If you knew the effects produced by "liqueur de Vilate," you can form an idea of the power of this water.

You must therefore remember that there might be disadvantages in certain cases in atomizing some mineral waters. Those that are generally employed have not this topical power. They are sulphur waters of all kinds, alkaline and saline waters, and mixed saline and arsenical waters. The sulphur waters are waters containing sulphide of calcium and sulphuretted hydrogen, also mixed sulphides, like the Eaux Bonnes, which are intermediate between the sulphides of calcium and of sodium; they are also waters containing sulphides of sodium, and calcium and alkaline at the same time.

None of these are very powerful in their topical effects. Hence there is great utility, great profit, and almost no inconvenience where precautions are taken, in making use of them for inhalations. In a great number of establishments, only to mention those that are French, we see these inhalations of atomized waters long established and on a good footing. Among sulphur waters, properly so called, we have Pierrefonds, Enghien and Saint Honoré; in the Pyrenees, Eaux Bonnes, Luchon and Canterets; Uriage, which is a saline and somewhat sulphurous water. Similar to it is that of Ussel, in the department of the Gard.

We have in France a number of mineral waters which possess a double mineralization; they are both sulphurous and bituminous, that is, they contain a sort of fluid bitumen. These possess profitable application to a great number of affections, particularly those of the skin.

I will not say that they are very agreeable to take, but bathing in them produces excellent effects. They are also used in the atomized form, and they answer a double purpose—they produce a useful astringent action and particular topical effects, due to the sulphurous principles which they contain.

We also have alkaline waters in abundance: there is Vals with its forty-odd springs, which offer a graduated scale in fixed principles from 50 grs. to 9 grs. in each litre. There is Vichy,

the queen of those waters. In these two great watering stations they have established inhaling halls for atomized water, which render good service in affections of the throat, and especially in arthritic cases. You are aware that gout shows great variety in its effects. There are a certain number of affections due to this diathesis, which develop in the direction of the respiratory and digestive organs; in these cases atomized alkaline mineral waters render real service.

We also have a certain number of springs which I have designated under the name of *mineral nymphs*, which produce all the salts that exist in the serum of the blood. Take water from Saint Nectaire and serum of blood, and you will find them to contain nearly corresponding quantities of salts. These waters, which are no recent discovery, are pointed out to us by the most ancient tradition as serving to repair exhausted organisms and to improve persons afflicted with scrofula. They are also used in atomized form in affections incident to this prevalent diathesis. As similar in effects, I shall mention Royat and la Bourboule. These are comparable to sea water. At Arcachon, at Fécamp and at Trouville, we have atomizing and inhalations of salt water in a more or less nebulous condition.

Let us sum up what we have just said with regard to the precautions to be observed in atomizing mineral waters.

The water must be at a mean temperature of from $+ 25°$ to $+ 32°$. It must be as finely atomized as possible, so that it may be in the highest degree penetrating. Furthermore, as the apparatus has not always the perfection you might desire, and as you must always suppose that you may meet with imperfect atomizing, the patient must be covered with a gown made of some impermeable material. Only under those conditions will you secure the efficacy of the remedy without the possible liability of taking cold, to which persons were formerly exposed.

I must now tell you of some of the applications of atomized water, and of one in particular, quite recently introduced. This is the inhaling of a solution of sulphate of quinine by patients who could not take it by the stomach.

It often happens that following a fever that has required large quantities of sulphate of quinine, there is developed such an intolerance of the stomach, that it becomes unable to retain the drug which, however, may be necessary for the cure of the patient. Prior to our having bromo-hydrate of quinine, which is an inoffensive form of quinine for introducing into the subcutaneous cellular tissue, efforts were made to devise a plan for the introduction of the sulphate otherwise than by way of the stomach; among others, inhalation of quinine was suggested.

Mr. Ancelon caused a solution of 500 grains of water containing 1 grain of sulphate of quinine to be atomized at the home of a patient in two sittings during the day, and he had the satisfaction of not seeing any return of the fever, which yielded as it would have done to doses taken into the stomach. This example has been imitated by Mr. Bujon, who has used the same process and obtained a sudden cessation of the fever. These facts are at present less interesting, because we have the hydro-bromate of quinine, but, nevertheless, they still retain a real physiological interest.

Atomization of artificial solutions or of mineral waters, has been employed for other purposes than inhalations, as in ocular affections of old standing, which have resisted other means. These douches upon the opened eye-lids have given good results. Mr. Pigeaux has attempted treating cases of endometritis by atomized solutions of nitrate of silver. He has met with comparative success. The plan has some advantages: in the first place, an atomized douche has not the force of an injection, properly so called; it does not give rise to accidents from fluids entering the interior of the cavity of the tubes, and in consequence it does not produce those more or less serious and at times fatal accidents induced by active substances; besides, by the very fact of this atomizing process, the whole surface of the uterine cavity is acted upon by the medicament.

If a moderately concentrated solution is used, an atomization is obtained which is beneficial in those cases in which the mucous membrane presents a resemblance to velvet, and is highly vascu-

larized and bleeding. When there are fungosities, it is evidently better to follow Mr. Richet's process, which is no other than that of Lallemand, of Montpellier, and which consists in the introduction of a caustic holder, so shaped that the whole surface is cauterized.

I add but one word more, in relation to what has been called "aquapuncture." The idea was conceived of using a very fine water jet obtained by the aid of pressure of not less than four or five atmospheres, for the purpose of percussing the surface of the skin, and obtaining not merely a pricking sensation, not only a bright redness on the spot which was the seat of percussion, but also for actually perforating the skin.

Some years ago I gave my audience an opportunity of witnessing these effects, by piercing in their presence leather of considerable thickness. Hence, as you see, this is rather a violent process, and one whose action is difficult to measure. And to obtain what? About the same effects as by the aid of the most easily handled topical irritants, like puncturing with needles—and, moreover, often without any therapeutic results. It was my duty to mention this absolutely useless process, which anyhow, we may say, is forgotten by the majority of the public.

CHAPTER XI.

Open Wounds—Cutaneous Methods.

Absorption through Wounds; *Absorption by the Serous Cavities.*

Cutaneous Absorption—Fallacy of the arguments advanced in favor of absorption through the unimpaired skin; refutation of those arguments.

GENTLEMEN:

We have concluded tne study of the mucous tracts, as avenues for the introduction of medicines. I have now a word to say on the pseudo-mucous membranes, which are those found in mucous tubercles, in burrowing wounds and in fistulas.

It may be said that these are, from a functional point of view, true mucous membranes, which may become surfaces for absorption. At times, this is very obvious. When, for example, surfaces covered by mucous abrasions of syphilitic origin have been cauterized, these surfaces being of great extent, it has happened that acute hydrargyrism of the most intense kind has been excited, together with painful and fœtid stomatitis, followed by unpleasant sequelæ. This absorption, however, becomes a favorable circumstance in effecting a thermal cure. It has been observed that in these thermal cures, which are effected with saline waters holding iodides and bromides in solution, the patients who derive the greatest benefit are precisely those who were most seriously affected. Thus, you send scrofulous patients to seek a cure either at Kreuznach, or at Salins, or at Salis de Béarn, and you observe that those patients are the most relieved who presented in appearance the most serious accidents. If they only have, as yet, ganglionic enlargements, they will no doubt derive benefit from tonic mineral waters; but if they have fistulous

courses, ulcerations on the lower limbs and on the neck, by having them plunged into these stimulating waters (to which are added what are called the mother liquors, which are more highly iodo-bromized than the water itself,) these patients will derive really wonderful benefits. The ulcerated surfaces are soon modified; they regain their color; the tissues become healthier, while, at the same time, the secretions become more regular and assume a more satisfactory character. The patients owe these improvements in their conditions to the presence, on the periphery of their bodies, of surfaces as capable of absorbing as are the mucous membranes themselves.

There are also circumstances in which the serous cavities become a seat for the absorption of medicaments. For example: it not rarely happens that when an injection is thrown into the vaginal tunic, of a mixture of water and tincture of iodine, such rapidity of absorption is sometimes developed by the serous membrane which has been touched by the injection, that the patients are taken with real, genuine, acute iodism—watering of the eyes, intense coryza, and such an obstruction of the nose that they are hardly able to breathe.

I shall now speak of medicamental introduction by the cutaneous periphery. There are distinctions here to be made. At times, the skin is unimpaired; again, it is deprived of its epithelium; at other times, the introduction is made within the thickness of the dermis; or, finally, by the subcutaneous cellular tissue.

Let us first speak of the introduction of medicaments through the unbroken skin. A debated question here arises. Is the unimpaired skin an avenue of absorption for medicaments; and if it is one, for what substances, and in what quantities? This question has been solved in very different ways. There are circumstances which prove that absorption takes place through the unimpaired skin, and there are others which demonstrate the contrary. We must distinguish the chaff from the good grain. We must always, to some extent, refer ourselves to physiology, and you know it is generally in that way that I commence the

study of medicaments. What does physiology teach us as to the possibility or impossibility of absorption through the skin? It teaches us that the skin is provided with a very delicate apparatus, and is a vigilant sentinel, which not only warns us against what may harm us, but also that it is a medium by the aid of which we have the sentiment of self so strongly developed that whenever its sensation is abolished, we lose this sentiment. It is under these conditions that Saint Theresa and other persons have believed that they no longer had a body distinct from that of the universe, but that they had united themselves with the divinity. The skin is intended to protect the rest of the body, and you know how great is its protecting power, since when an injury has produced considerable lesions beneath it, it may remain intact, or at least present much smaller lesions. The skin is at the same time an organ for secretion, but it is an organ for excrementitious secretion; what it ejects is not destined to re-enter into the organism. It is an annex to the respiratory apparatus, not that the phenomena which take place upon the surface of the skin can be compared to those of cutaneous respiration among batrachians—no; but the skin is nevertheless an organ through which interchanges are made. For this reason it is necessary to recommend cleanliness, baths, frictions. Keeping up the cutaneous function is doing an important service with regard to hæmatosis itself. From what we have just said of the physiology of the skin, can it be supposed that it is a very energetic organ for absorption? No; and even it may be said, *a priori*, that it can only be a surface of absorption for substances analogous to those that are exchanged, in a normal way, through its pores.

You will see that what physiology indicates as probable is demonstrated by the observation of facts, and consequently you see how useful it is always to take it as our guide and our beacon in all pathological and therapeutic questions.

I was saying that we could only look for the absorption of volatile or gaseous substances. And yet, from all time, it has been the custom to apply upon the skin all the substances which the stomach refused to accept, and experiments show that a cer-

tain number of successes obtained led easily to entertaining illusions upon its absorbent powers.

Four lines of argument have been advanced in support of the reality of this absorption. It was said that upon the application of medicaments to the cutaneous periphery, it has been noticed that similar physiological and therapeutic effects were produced, as would have been the result had the introduction of these same medicaments taken place through the stomach. Again it was said, that there was a certain proportion of the substances applied upon the skin which had disappeared, as though absorbed by it. It was added that when substances with which bodies were in contact, were in sufficiently considerable masses, they could be absorbed in such proportions that there would result an increase in the weight of the body. Finally it was stated that in a certain number of cases substances applied to the cutaneous periphery had been detected either in the blood or in the urine.

These are the four lines of argument invoked in support of cutaneous absorption. We shall take them up singly, to ascertain their value. Let us speak of effects said to have been obtained by the aid of medicaments applied to the periphery. There are here certain facts which must be reviewed.

At a remote period it was observed that baths or poultices laden with emollient or narcotic principles, and that topical applications, consisting either of cold or of astringent substances, produce positive effects. And it was said that if those substances applied upon the abdomen or on the periphery of the body had determined, some soothing and sedative phenomena, others stimulating and resolvent phenomena, it was probably because these substances had penetrated the system, there to produce the effects of which they were capable.

They forgot but one thing—that there is a *sympathy of continuity and contiguity*, as John Hunter called it; that there are incessant exchanges of stimulation and of sedation between the tissues of two neighboring regions, by virtue of what I have designated by the name of *polarization*. And that, I repeat, explains in great measure the calming or tonic phenomena pro-

duced by the application of certain substances on the surface of the body.

For example, if it is desired to allay a colic, a warm poultice is applied, and it is by some believed that the poultice is capable of producing a deep sedative effect, by the penetration of its constituents. No; it has been obtained by the process I have just indicated, and by reflex action, for which, however, too much importance has been claimed. You may read Schiff's experiments, read Vulpian's work, and you will see how evident is the existence of reflex phenomena between the different peripheric and the deep-seated regions, and how one side of the body is in sympathy with the other side. Already Brown-Sèquard had pointed out that when one hand is cooled the other is cooled also. But here a distinction is to be made: When the excitations are of very great violence, contrary phenomena are shown on the part of the deep-seated organs. If an intense cold is applied, there is produced a real paralysis of the deep-seated vessels in the parenchyma of the internal organs.

This explains those "repercussions" which are produced when intense cold has been applied to the periphery. On the contrary, when there is a moderate peripheric impression, whether its nature be to produce a relaxation of the vessels or a vascular contraction is of but little moment; it is an analogous phenomenon which produces itself within the organs. If, for example, you apply upon the abdomen a moderately cold body, you will contract the vessels in the deep-seated parts. If you apply upon it something warm, which gives rise to greater capillary vascularity, an analogous phenomenon will be produced in the deep parts. You then understand how it is that by the agency of these reflex actions, substances which exercise no actions but through their physical qualities, may determine sedative phenomena within the depths of a region upon which they are applied. Purgative effects have been spoken of as produced by the external application of certain substances, and some of the most illustrious names are quoted in support of facts of this kind, as those of Haller and Sœmmering, and also of Seguin, whose name is more modest. It has

been said that by the aid of drastic substances, such as calomel, castor oil or croton oil, applied on the cutaneous periphery, energetic purgative phenomena are produced; that other substances applied upon the skin have induced the expulsion of helminths. Even neutral salts have been supposed capable of acting by way of the cutaneous periphery.

These are statements, of which two categories may be made—those which are altogether impossible, and the others which, without being impossible, are altogether improbable. I apply this to the story of the neutral salts. Supposing that these salts when deposited on the surface of the skin, had the power of producing effects through it, let us see if, when absorbed, they could determine the purgative effects attributed to them. No. We know ever since the experiments made by Moreau and repeated by Rabuteau, and we have also learned by clinics, that when neutral salts are introduced in the blood, and go to increase the proportion of those which are already there, not only they do not determine purgation, but they produce constipation. I say that we have known this for a long time, and all physicians who practice in the neighborhood of mineral waters know that when waters highly charged with salts and capable of purging, are taken in such proportions that purgation does not immediately follow, whenever, in a word, the subject resists their effects, not only the subject is not purged, but he is constipated. That is what happens at Carlsbad, at Hamburg and at Kissingen, when those waters are taken by half glassfuls, and they do not purge. Persons who had a stool once a day no longer have any. These waters are both purgative and constipating, according to the following process:

The salts not being eliminated are absorbed; they go to swell the proportion of salts in the blood, and thereby oppose themselves to increased serous secretions.

This is what we likewise observe at the French thermal stations, which, in lesser numbers, are gifted with purgative properties. We also know that the different waters used as purgatives, such as Pullna and Siedlitz, and which are in abundance at the present

day, are constipating, when given in insufficient doses to produce purgative effects. Freiderichshall water is even given as a restorative, as a means of increasing the proportions of salts in the serum, in cases of albuminuria. Here are cases, therefore, in which the phenomena that have been attributed to cutaneous absorption could not have taken place.

There are others whose occurrence is improbable. Here is rhubarb, a drastic root, of which a large quantity is required in order to purge. How can we admit that applied upon the skin, it could have produced physiological effects? The case is not altogether the same with calomel and croton oil. Calomel is a mild sublimate. It is, therefore, a volatile substance, and if it is a volatile substance at $+ 37.5°$, it can be sufficiently volatilized so as to be absorbed by the respiratory organs. But supposing that calomel could have been absorbed in small quantities? It would have, at most, produced alterative effects. There is, besides, a coincidence, against which we should be on our guard, to wit, that of a natural clearance, but which is credited to the substance employed. Great stress has been laid upon the effects of croton tiglium applied on the skin. It is a complex substance, which contains both a fixed oil and an essence. It is therefore evident that if an extensive friction has been made and if the patient remains covered up in bed, this may determine phenomena of irritation in the tract of the digestive duct. But here, I think, fallacious coincidences have been met with.

Other medicaments have been spoken of as capable of being absorbed by the skin, among them mercury. Yes, the mercury which exists in mercurial ointments is absorbed, and we shall see further on in what way. Although mercury is not very volatile, it emits vapors at 15° below 0, hence, still more so at 37°.

Consequently it is readily understood that when an extensive friction is made, as in peritonitis, or in the case of syphilitic patients, in both arm-pits, the patient may absorb sufficient vapor to exhibit the diffused effects due to mercury. But we shall presently see that it is also absorbed by the skin.

Great stress has been laid upon certain cases of poisoning said

to have been produced either by extract of belladonna, or by poultices of tobacco leaves, applied upon the abdomen. There are here two causes of error. You cannot prevent persons upon whose abdomens extract of belladonna has been applied, from putting their hands there, and then carrying them to their eyes. This would account for the pupillary dilatation. I add, that the alkaloids from belladonna and from tobacco are volatile substances. Therefore, I think no importance should be given to facts of this kind, for the purpose of showing cutaneous absorption.

Iodide of potassium is also a substance which has given rise to modifications in the urine, indicative of its passage. We shall see how this phenomenon is produced. But at all events it is not iodide of potassium in solution that can be absorbed. Arsenic, cantharides, tartar emetic—these are all substances said to have been absorbed. But I would have you remark that all those substances are only absorbed after *friction*.

With regard to cantharides, there is, in the first place, a more or less intense inflammatory irritation, a secreted serosity which takes up the cantharides, after which the dermis absorbs the serosity. Here absorption takes place of a serosity laden with cantharidine, and, besides, the skin is no longer unimpaired.

The same is true of arsenic, which produces inflammations and eschars. It leads to mortification, but not to the chemical transformation of the tissues, which are still recognizable, after having been killed by arsenic. But, anyhow, it forms eschars, and when once it has thus penetrated it can be absorbed by the vessels in connection with the eschar. I shall say as much for tartar emetic, which gives rise to those pustules which you all know, and which is likewise only absorbed by means of frictions. Consequently, all this does not apply to the unimpaired skin, and hence is of no applicability to the question now occupying us.

I come to the argument concerning the disappearance of a certain quantity of the substance placed on the surface of the skin. It is Seguin, especially, who has introduced this new notion. I do not think that he has rendered thereby any great service to science, or adduced any positive facts to support it. He im-

merses his arm in a local bath, and he observes that when the bath has been sufficiently prolonged, the weight of its water having first been ascertained, there is a loss in that weight. Certainly, there must be a loss. There you have an arm at a temperature of 36°; you immerse it in a local bath; of course, a certain proportion of the water must be volatilized. This experiment is absolutely worthless.

He also made others, which consisted in placing on the skin, under watch crystals, so as to maintain them in close contact with it, scammony resin, calomel and tartar emetic. After the contiguity had lasted ten hours, he found the scammony had lost one-fourth of a grain, the calomel two-thirds, and the tartar emetic 5 grains of a total of 72 grains. Do you believe, gentlemen, that the disappearance of gr. .¼ of scammony proves anything? It is only necessary that the spot should have been carelessly wiped off; gr. .¼ is something so very small.

In the other case, I cannot admit that 5 grains of tartar emetic could disappear without considerable phenomena having resulted therefrom, such as pustules with central eschars. All these effects should have been produced if the action upon the skin had been really energetic, and sufficient to explain the disappearance of gr. 5 of tartar emetic.

I believe that there were errors in the weighings. There may have been imbibition by the epithelium of the solution, and an impossibility of removing the substance—owing to adhesion to the epidermic coating; perhaps, even destruction of the salts, but assuredly there was no absorption. All the experiments which we make at the present day demonstrate in a peremptory way, that absorption, under those conditions, would have been impossible.

But there is another grand argument, the main dependence of those who admit cutaneous absorption. In a bath the body increases in weight. This increase is not enormous; it is from 40 to 50 grammes. You will tell me that this is a good deal; but I maintain that it is little, if you reflect upon the surroundings,

which cannot fail to remove from the bath a certain proportion of the water it contains.

You know that after a bath that has lasted an hour, and even less, your skin is all wrinkled, because the epithelium is tumefied; you have only to look at your fingers; the epithelium has become white, opaque, swollen. The result is a corrugation comparable to the cerebral convolutions, proportioned to the degree of imbibition of the epithelium. Therefore, the epithelium of the palm of the hands and the soles of the feet imbibes, and you can form no idea how much water this imbibition represents. When you will happen to have under your care patients suffering from intense scarlatina, from whom you can remove a gauntlet formed out of the epithelium, remove it, and after having dried and weighed it, wet it and weigh it a-fresh. You will then see, if you multiply the result by the surface of the feet and hands, that the amount obtained is almost sufficient to account for the quantity of water that has been absorbed in a protracted bath.

I have made this experiment, and have ascertained that the amount is considerable. Messrs. Delore and Hébert repeated the experiment, and came to the same conclusions; that is, that according to all experience, the water which impregnates the epidermic coatings of the hands and feet, together with that which remains on the surface of the body, is sufficient to account for the increase in the weight of the body. Besides, when you come out of a bath, believing yourself immaculate, if a shampooer takes charge of your person, he will prove to you that you still have grammes of epidermic matter on the body. This matter is no longer alive, but as it adheres on the surface of the skin, it is still capable of absorbing a considerable quantity of water. That is, therefore, another argument which we are obliged to lay on the table. But there is the scientific argument. This is, as I told you, the presence in the blood, or in the secretions, of substances deposited on the surface of the skin. There have been a great many experiments made, and with different substances, to prove this passage into the blood. Ferro-cyanide of potassium, which is often used because of its reactions, has been employed, and it

is said to have been detected in the blood and in the secretions. I rest satisfied here, with the expression of a doubt. I believe in the possibility of absorption in certain cases, but to establish in a rigorous manner that it had been absorbed, it is not sufficient that the thing is possible, especially as it has been proven, that there is in the economy a substance more or less analogous to cyanide of potassium. Remember that there are sulphocyanides in the saliva, and that Prussian blue may be formed at the expense of the blood.

You see that those investigations, based upon minute quantities of substance, are surrounded with uncertainties. On this score, I reserve my doubts.

It is said that the coloring matters of madder and of rhubarb have also been detected. For us who know how numerous are the coloring matters in urine, who know that there is a urinary indigo, and substances analogous to those that are derived from aniline, we cannot attach importance to reactions that are at least doubtful and made under such conditions.

It has been said that water penetrates not only because we find that the body augments in weight, but because we observe an increase in the urinary discharge. Nothing of the kind takes place. The urinary discharge is increased, not because a greater quantity of water has penetrated, but by virtue of reflex actions which bear upon the sensibility, and on the renal vessels, and vascular tension. This is so true that at the same time that protracted baths are regarded as giving rise to more urine, they give rise to alkaline urines. Odd, indeed, if those alkaline urines had shown themselves following Vichy water baths. What a fine argument! It had then been evident that not only water was absorbed, but it also carried along its salts! There is but one misfortune; it is, that with alkaline baths no alkaline urines are given, but they appear after baths containing nitric acid. Therefore, it is not the absorbed alkali which has given the reaction to the urine. I merely add that the occurrence is still of difficult interpretation. The fact is true; it cannot be denied; it has been witnessed by several distinguished observers. All those

who have submitted themselves to protracted baths of this kind have observed it.

It is probable that under those conditions a phenomenon takes place comparable to that which exists in convalescence. In this state, there is a period during which the urines are always alkaline, so much so that when you find a patient in full convalescence, with reduction of temperature, and you ask for the urine, it is uniformally alkaline.

It seems to me that protracted baths produce upon healthy subjects conditions somewhat, or perhaps altogether, analogous to those exhibited by convalescents, in whom there is a profound sedation of all organic acts.

But there are other facts which have had greater notoriety, and which appear more precise and more scientific. They are those observed by Mr. Willemin, and by the regretted Hirtz, of Strasbourg. These two talented and conscientious men applied themselves to examining what took place when a subject was immersed in a bath containing sublimate, or iodide of potassium, and they came to the conclusion that the skin absorbed, contrary to all adverse testimony. They examine the urines of persons who have remained in a sublimate bath, and find nothing in them. They make their observations upon baths containing 100, 200, 300 grammes of iodide of potassium, and often note negative results and sometimes positive results. You, no doubt, suppose that after this they should have said to themselves the skin is not an available absorbent. Not at all; they adhere to positive facts, lay the others aside, and conclude that the skin is a comparatively fair absorbent, and that baths can introduce into the economy more or less considerable quantities of the principles with which the water is laden.

I shall discuss this conclusion in the next lesson, and show you how faulty it is.

CHAPTER XII.

Cutaneous Method.—Baths.

Cutaneous Absorption [continued].—Explanation of contradictory facts and opinions.

The skin absorbs under certain conditions.—Action of fatty bodies.—Volatile substances.—Action of the law of gaseous diffusion.

Processes adapted to favoring absorption through the skin.—Special activity of certain regions.

Medicinal baths; their value.

Gentlemen:

Mr. Roussin[1] has demonstrated that by placing yourself under favorable conditions, the iodide of potassium contained in a bath is never absorbed through the skin. That is to say, if your skin is perfectly unimpaired, if you wipe yourself thoroughly, and especially if you take an ordinary bath after the iodized bath, there will be no iodine in the urine. On the contrary, he has demonstrated that when you make use of a solution of iodide of potassium in the proportion of a tenth, and apply it upon certain regions of the body, allowing it to dry upon you, or else, if you pulverize iodide of potassium and dust it on your undershirt, under those conditions iodine is always observed in the urine.

How, then, explain such contradictory facts? To my mind, the explanation is a simple one; here is what takes place: after you have, so to say, daubed over the surface of the body, the axillary regions, for example, with a concentrated solution of

[1] Roussin. Double Poisoning by Schweinfurth Green. New Experiments Relative to Cutaneous Absorption. (Ann. d'Hyg., 1867, 2d Série, tome XXVIII., p. 179.)

iodide of potassium, or when you have applied to the periphery powdered iodide of potassium, at the end of a certain time you can no longer find it. Do you know what color is assumed by ointment made out of fresh lard and iodide of potassium? This ointment, which at first is white, gradually becomes yellow, then changes to a more or less reddish-brown. What is it that takes place in the case of this ointment, which finally becomes brown and of a disagreeable odor? This is what has taken place: however fresh was the lard, it has finally grown rancid, and the fatty acids have gradually liberated the iodine previously combined with the potassium. It is iodine that is liberated, and it denotes its presence by its coloring and its smell. When you apply iodide of potassium on the surface of the skin, the same phenomenon is produced and in the same way. Remember that perspiration is an acid liquid containing volatile fatty acids of sufficient energy to act upon litmus paper. When iodide of potassium is in contact with the skin, it is decomposed and iodine is liberated. But it is a volatile substance, consequently we can apply to it the remarks we made at the opening of the preceding lesson, when, in considering other substances of a similar kind, we supposed it was possible for them to be absorbed by the respiratory organs.

We therefore say that it is possible that the iodine set free under the influence of the acids from perspiration, should be absorbed by the respiratory organs, and not by the skin.

This leads me to tell you that iodine in the metalloid state can really be absorbed by the skin.

Thus far I have only shown you negative results, and given you to understand that all anterior conclusions were hasty and faulty. I shall now demonstrate to you that there are substances which are absorbed through the skin.

For this purpose iodine supplies us with the most perfect means of demonstration. When iodized cotton is applied, and the region it covers is enveloped in an impervious dressing made of adhesive plaster or thin layers of gutta percha, and finally bound over with a bandage of flannel, so as to maintain the

whole and exclude the air, we find that iodine is absorbed, and it shows itself in the urine after a lapse of time.

I must confess that when I made these first experiments, originally with tincture of iodine, I was especially impressed with its penetration into the economy and its diffusion, when the epithelium covering the region appeared to me to have suffered deep alteration. But I have since made other experiments, from which there results the possibility of two cases presenting themselves, the one to which I had at first attached importance, and another, which is the following: you may make the application around the hand, surround it with an impervious muff, and absorption will take place although nothing on the dorsal surface of the hand, hence much less so on the palm, will the next day reveal the existence of any lesion of the epithelium; and the proof is, that there is no desquamation even with the most concentrated tincture of iodine. There are, therefore, cases in which the absorption of iodine takes place, although the epithelium is unimpaired.

It is very easy to prove the existence of iodine, or, at least, a combination of iodine, in urine. This very simple process consists in pouring commercial nitric acid, little by little into the glass containing the urine to be tested, and then dipping to the bottom of the glass a piece of paper. Provided that this paper be of finely divided cellulose (it is not even necessary it should be starched,) it will, under the influence of the acid, liberate the iodine held in combination as an iodide, and that will then impart a blue color to the paper. It is therefore very easy at present to demonstrate that iodine has been absorbed through the skin, even without any alteration of the epithelium. What takes place with iodine may occur alike with all similar volatile substances, and this confirms the opinion derived from physiological considerations, which I spoke of at the opening of the last lesson.

I told you the skin was a vicarious agent of the respiratory organs—it absorbs gases and volatile substances alike. Of this we have an almost rigorous demonstration in the mercurials.

As you know, I have sometimes caused mercurial frictions to be made in the palms of the hands, care being taken to envelop these in an impervious dressing, and I have thus obtained absorption and positive therapeutic results. A greater number of experiments are desirable, but there are few syphilitic patients ready to lend themselves to this treatment. However, I repeat, that at present it is fully demonstrated, rigorously in some cases, in others with a near approach to scientific rigor, that volatile substances can be absorbed by the skin. Thus formic and valerianic acids, ammonia, and such volatile substances as musk, camphor, castoreum, and others containing these principles, may be absorbed by the sudoriparous glands. Likewise all volatile organic alkaloids, as those from the hemlock, and generally all those from the poisonous umbelliferæ, cicutine, coniine and conicin. The same is true of nicotine, atropine and duboisine, a new alkaloid obtained by Gerhart, in England, and in France by M. Petit.

The question is, how does this absorption take place? I gave its theory long since. It has been lately renewed in Germany, I was about saying, taken from me, but I prefer believing that it has been re-discovered. As early as 1869, I published an article on this subject, showing we could here apply the law of gaseous diffusion, which says: when a gas penetrates into a confined space, it diffuses itself in equal proportions throughout the whole atmosphere of that space. This explains how gases coming from the blood are diffused in the atmosphere, while those from the atmosphere, diffusing themselves in the sudoriparous ducts, may be absorbed by the glands. It is, therefore, the theory of diffusion which I have applied to particular gases. Newman, in 1871, expressed the same thought, and explained, by this diffusion, the action of gases. This proves the correctness of my opinion.

Are only volatile substances absorbed through the skin? The skin is capable of absorption when active substances are in solution, or in an intimate mixture equivalent to solution. Thus camphor is not soluble in water, yet we have camphor water,

that is, camphor vapor in a molecule of protoxide of hydrogen. There are substances also, which, although insoluble in fatty bodies, yet enter into such intimate mixture with them that they are carried wherever these bodies go. This is the case with many liniments. Active substances when in solution in fatty bodies, may penetrate through the epidermis in contact with the superficial vascular elements of the dermis, and be more or less absorbed.

The more clearly to understand these interesting phenomena, you have only to remember what happens with a filter which has first been saturated with oil. When you throw upon it a mixture of a fatty body in an aqueous solution, the aqueous solution remains and the fatty body filters through. The same happens when a mixture consisting of an aqueous matter and a fatty substance holding in solution active principles, is brought in contact with the epidermis more or less impregnated with fatty matters, the fatty matter passes through this filter, but the substance in the aqueous solution is not admitted. That is the first case. Another is, when this epidermic barrier is either made thinner or modified in its chemical composition so as to become permeable. It may be made thinner by frictions; hence these have often been recommended for the purpose of favoring the absorption of substances incorporated with fatty matters; such frictions, when by a vigorous hand, sometimes result in an abrasion of the epithelium. Absorption then takes place through the superficial coating of the dermis.

But there are other methods by which the thickness of the obstacle may be reduced. For example, the epidermis is not entirely composed of living layers; there are on its surface old layers, either dead or in process of separation. Alkalies are an excellent agent for the removal of this layer which forms an emulsion with the fatty matters of tallow, hence it is advisable to wash with soap the place through which absorption is desired. The epidermis may also be made more permeable by the action of acetic acid on the surface of the body, this acid, as you know, possessing the faculty, if not of dissolving at least of

softening, and hence of greatly reducing the state of imperviousness of the epithelial cells. So energetic is this action that there are popular remedies for the removal of callosities, corns and bunions, which consist mainly of acetic acid.

There are also other methods, such as rubefacients, which are often recommended for the purpose of favoring cutaneous absorption. By their use the skin first reddens, and the small vessels are dilated, but this is not the important feature. Following this artificial inflammation there is a considerable desquamation of the epithelium, which at times falls off in large shreds, and there remains a reddish surface covered over with a thin epithelium, which absorbs rapidly. Such are the ways of reducing epidermic resistance. The epidermic coating may also be made permeable by freeing it from the substances that cover it. For this purpose ether, chloroform, sulphide of carbon, in fact all substances acting as solvents of fatty bodies may be used. Protracted maceration in water, as in the case of baths lasting two hours, gives opacity to the epidermis, which becomes more permeable, and may thus give passage to a small proportion of the substances held in aqueous solution. This would justify those who believe in the penetrability of active substances dissolved in water. It is of no practical benefit, however, because the quantities of active substances introduced are infinitesimal, and no reliance can be placed on their effects.

The whole discussion may be thus summed up: gaseous, or volatile substances are highly absorbable by the skin, and they are still more so when more decidedly gaseous or under the form of volatilized substances. On the contrary, substances simply soluble in certain vehicles pass through the skin with comparative difficulty. When soluble in fatty bodies, they may penetrate to the superficial net-work and be absorbed. When dissolved in water, absorption is almost impossible, or takes place very slowly. Here, however, a distinction comes in, which I have already made.

There are regions in which the epidermis does not present so serious an obstacle to the absorption of substances; these are the

hands and the soles of the feet. Here there are no sebaceous glands, no fatty coating, hence favorable conditions for gaseous and aqueous absorption exist, more so for the former than the latter.

I may say as much of other regions, like the groin and the arm-pit, both often selected by partisans of the cutaneous method. Those regions are not under the same conditions as others, as in place of sebaceous glands there are bunches of glands, well described by Ch. Robin,[1] secreting a product which is not sebum. Consequently, these glands do not lubricate the epidermis, as is the case in other regions, and the absorption of substances dissolved in water is therefore much more active.

The practical indications for grading the different substances which may be placed in contact with the cutaneous periphery, are as follows: Aqueous solutions of active principles, taken from the mineral or organic kingdom, should not be entrusted to cutaneous absorption, unless they contain very active substances like acetic or hydrochloric acids, but as these are highly active, from a chemical point of view, patients are not usually subjected to them.

Volatile substances may be absorbed through the skin. A solution of morphine, or of nicotine, may be applied to the periphery of the body and absorption be possible, since the organic substance is volatilized; whether it passes through the respiratory organs or through the sudoriparous glands, it can enter into the economy.

Nothing should be expected from that long list of methods for which good results are claimed, such as poultices containing narcotic substances, lotions, fomentations and local baths. All those give nearly negative results. Almost as much may be said of general baths, and this is important, because you daily prescribe baths with arseniate, or carbonate of soda, or of natural mineral waters, always under the belief that a more or less active absorption will take place, producing effects similar to

[1] Robin. Medical Dictionary, (14th ed.) Paris, 1878, p. 679. Article, "Glands."

those which would have followed the introduction of those active principles through the digestive organs.

The experiments made at Strasbourg and elsewhere only tend to continue this general error. I cannot uphold that view, and in this I am in accord with numerous authorities, particularly with almost the whole Medico-hydrological Society, in which a commission was appointed, which has reached conclusions similar to those I now announce; that is, that there is no absorption from baths, and it is needless to expect any. Therefore, I unite with Scoutetten in saying that arsenical baths should not be prescribed, with the belief of obtaining general results, and I add, except it be in the case of women, or of subjects affected with more or less intense cutaneous diseases, from an anatomical standpoint, which have so modified a certain extent of the periphery as to render absorption possible.

Let me explain. If you have a patient affected with eczema, his skin is as if he had a blister. Under those conditions, he can absorb wonderfully well, and you should even exercise caution, for if too large a quantity of active principle is added to the bath poisoning may follow. Evident phenomena of absorption may also be manifested among women, chiefly among those who have extensive mucous surfaces, in whom the labia pudendi are largely developed. This surface is in itself sufficient to absorb active principles. Hence some reservations are to be made with regard to absorptions which may take place in a normal way with women, and accidentally with subjects affected with cutaneous diseases. But as to arsenical baths for subjects affected with nodular rheumatism, absorption only takes place when the skin is more or less deprived of its normal epidermis.

The use of substances dissolved in fatty bodies may be continued without placing too much dependence upon their absorption and diffusion. These may be facilitated by repeated and prolonged frictions, tending to render the deep-seated layers more permeable to active substances. This constitutes a method which was offered as a substitute to all others. With these mechanical processes may be included sinapisms and all rubefacient methods.

With regard to gases and volatile principles, I have but to confirm what I have already said as to their facility of absorption. This explains why extract of belladonna, applied on the abdomen, has shown marked effect upon the eyes, without the patient's hands having been instrumental in conveying it there. Compresses of chloroform also produce effects when covered over with impervious tissues to prevent evaporation. They not only have an immediate irritating, topical effect, but an eminently soothing, consecutive action, which shows that the chloroform has penetrated into the region, probably, by absorption. For this reason you may advise carbonic acid baths. Thus at Saint Alban and at Kissingen these baths have a marked influence on the skin. Carbonic acid first produces a very perceptible stinging sensation, then a reduction of sensitiveness, proportioned to the degree of local asphyxia.

It is likewise because of this possible absorption that we so often make use of dry sulphurous, arsenical or mercurial fumigations. These last have lately recovered the importance they had lost. They were formerly one of the methods most frequently used in cases of secondary syphilis, but they were abandoned because of their difficulty. They are again in use, and without becoming a general method, will serve when circumstances forbid stomachic ingestion.

Even by associating mercury with aromatics, we cannot guard against accidents with persons whose stomachs are rebellious, or those in whom diarrhœa sets in when they take a pill. The subjects being already poor in globules, we cannot allow them to sink under the influence of the remedy. In such cases, fumigations are highly serviceable. They were formerly made with cinabar, and at present with calomel. Both methods, I believe, are good, even when there are no lesions on the skin, hence still better when those exist. For this reason favor has again been given to mercurial frictions, which were the exclusive method of certain practitioners of the last century. These frictions render great service; they spare the digestive organs, and are remarkable for their decided and speedy effects. At times, a single

friction is enough to produce symptoms of hydrargyrism, and to modify syphilis. However, neither this method nor any other can replace the use of mercurial preparations.

The main objection to the cutaneous method is that the processes are often difficult to manage. It is easier to take a pill than a bath, and the ointments used are greasy and have a disagreeable smell. But the advantages are often considerable. Those processes save the digestive organs, and in a certain number of cases are prompt and safe in their effects, as we daily see in instances of syphilis.

CHAPTER XII.

Diadermic Method.—Hypodermic Method.

Diadermic Method—History.—Mayer's hammer.—Ammoniacal blister.—Precautions to be taken.—Its advantages and disadvantages.

Entodermic Method—History.—The life-awakener.

Hypodermic Method—History.

GENTLEMEN:

I have now reached the method to which I have given the name of diadermic or endermic. This consists in the introduction of medicaments through the skin deprived of its epidermis, but otherwise unimpaired. Blisters, although unknown to Hippocrates and his immediate successors, have been in use a very long time, and ever since the effects of vesical cantharidism have been observed, it is known that absorption beneath the epidermis is possible, since the serous fluid takes up the cantharidine, and is afterwards absorbed through the surface of the denuded dermis, thus conveying into the economy the active principles of cantharides, and giving rise to those very serious and often dangerous effects in the loins, known to us as nephritis and hematuria. These facts might have been observed a long time ago, but, in reality, the idea of reducing to a system the use of this method of absorption, belongs to Doctors Lambert and Lesueur, who, having combined their labors upon this new method, published their first results in 1823 (by Lesueur.) The endermic method received its name and full development in Doctor Lambert's work in 1828. In 1830 Gerard, of Philadelphia, who published the results of experiments made upon the leading substances then in use—opium, belladonna, hemlock, nux-vomica,

and many others used in the form of extracts or concentrated solutions, which he applied on the denuded dermis, had occasion to observe important physiological and therapeutic effects. But this method came into general use in 1833, after Trousseau and Bonnet published their work upon it, based upon cases in which morphine was used. From that date it assumed great importance in therapeutics, and I well remember the time when blisters, dusted over with morphine, were in as frequent use as hypodermic injections of active substances are at present.

Absorption by the endermic method is obtained by stripping the skin of its epidermis. For this purpose slow methods, like frictions, are to be discarded, but a blister is to be used. Still more expeditious processes are even preferable, if the physician desires to apply the remedy himself. Therefore, very active means of vesication are used. Cantharides might be employed when there is no urgency, but usually, preference is given to ammonia, or to Mayer's hammer, dipped in boiling water. Mayer's hammer, as so much used formerly, was at a temperature below 100°, and did not give rise to an eschar, but simply caused an ampulla. However, this process savored of barbarism, and no doubt the ammoniacal blister is in every respect preferable. Although this method has lost favor, yet it should not be entirely abandoned; therefore I shall give you some details.

The ammoniacal blister is prepared by the aid of what is called Gondret's ointment—(a mixture of lard and tallow, holding in solution the highly concentrated volatile alkali. There are two kinds; one for winter, another for summer use.) Or else, as has been recommended, the blister is made by applying upon the spot a flannel pad, dipped in concentrated ammonia. A disk of agaric dipped in concentrated ammonia may also be used, but it should be covered over with a watch crystal, or something of the kind, for the purpose of isolating the part to be vesicated. Another very simple process, recommended by Trousseau, consists in the use of a sewing thimble, in which raw cotton impregnated with ammonia is placed. Raw cotton does not readily imbibe aqueous solutions. To overcome this resistance it should be washed in

hot water, as Gayon advises, or better still, as I formerly showed, moistened with a very little glycerine, after which it will readily imbibe ammonia or any other liquid. The thimble containing the ammoniated cotton is then applied to the part to be vesicated, and maintained there for from three to five minutes, and sometimes more. It may even require a quarter of an hour; it depends upon the delicacy of the skin and the part which is being operated upon. With good ammonia, the delay of from three to five minutes will be found ample for almost all parts of the body. This may seem a short time, and the authors of the method favor a longer application. But it is not useful, and may be injurious. It is best to follow Trousseau's precept and remove the apparatus at the end of three minutes. No ampulla is formed, but the epidermis is more opaque, less smooth and somewhat wrinkled. This indicates that the operation is over, and it is needless to continue the application. The epidermis is detached and that is sufficient. When using very strong ammonia, if the application is continued too long it may produce an eschar, which would exclude absorption, since this takes place in an inverse direction from exhalation. If you give rise to excessive inflammation you create unfavorable conditions for absorption. This applies equally well to small and large blisters.

I shall never forget a poor fellow who was brought to the hospital suffering from cholera. He was not very ill, but he died from the effects of an ammoniacal blister of 0^{m} .25 in diameter, applied upon him in town. The eschar had included not only the skin, but the underlying muscles. You see there are disadvantages and even danger in using ammonia on an extensive surface. The apparatus must, therefore, be removed after from three or at most five minutes, and you will then notice that the skin is wrinkled. If this is the case, you remove it, because it is loose, and you have the denuded dermis, which is strewn with numberless little grooves caused by papillæ, the hair follicles and the sebaceous glands. This surface, which is of a somewhat bright rose color, immediately exudes a large quantity of serous fluid.

Before applying the morphine powder it is indispensable to

wait until this secretion subsides, otherwise the patient would derive no benefit, as the serous flow would carry off the active substance. After a time, when the surface is simply moist, the substance may be applied. It is covered by a disk of impervious tissue, and secured by strips of diachylon. This forms the first dressing.

There is a good cantharidized collodion prepared by a druggist in Lyons, which might be used to advantage. It produces vesication only at the end of a few hours, but it has the advantage of supplying its own dressing. Nothing is needed to protect it, hence its merits in the present question are self-evident. One the size of a twenty-franc piece could be applied, and after emptying the ampulla the active substance might be introduced as by inoculation; it would be protected by the collodion cap and require no further attention or dressing. Indeed, it might be used for fresh applications of the substance, because under the collodion the healing process is slower than in the open air. After this first operation there are precautions to be observed in order to secure absorption, for this method is either excellent or worthless, according to the way in which it is used.

When the second dressing is made, you will generally observe that the surface has changed its rose color to a grayish hue. Before replacing fresh active substance the old should be removed, otherwise absorption will no longer take place. The substances employed vary according to the object desired. When the purpose is to obtain the absorption of a sufficient quantity of active substance through so small a surface, preference is, of course, given to what are called alkaloids, but, as even at the present day, all plants have not yet yielded for us their alkaloids, we have at times to use very impure substances, which resemble molasses, but which possess a certain amount of activity. When necessity requires, we may use these active substances, whose intensity of action is known to us, although they are not absolutely pure. This method was formerly looked upon as presenting nothing but advantages. It however has a few drawbacks. It has the advantage of sparing the stomach, thus doing

away with those rebellions which bring on vomiting, and the consequent loss of the active substance.

By the endermic method, when you find that the effects produced assume greater intensity than you contemplated, you have it in your power to reduce absorption, and even to remove any portion of the substance which has not yet acted. By washing off the surface you can prevent the penetration of any fresh portion of over active substance, which might give rise to phenomena of intoxication, and you will presently see the value of this control over accidents. Another advantage of this method is its greater activity and intensity of action over the stomachic way. I constantly dwell upon this point, because it is of great practical importance. The stomach digests, that is to say, transforms everything introduced into it. Therefore medicaments given by way of the stomach only produce effects in the ratio of a third or a fifth of the bulk introduced. Consequently, if you introduce gr. 0.01 of morphine by the endermic method, you will obtain much greater effects than with a similar quantity by way of the stomach, yet gr. 0.01 is a medium dose for the stomach, and that usually used; it about represents the amount of active principle in a spoonful of syrup of morphine, hence it is a fair dose, which may be rather heavy by the endermic method.

I once attended a lady suffering intensely from ileo-lumbar neuralgia. I advised a small blister dusted over with morphine, which was obtained from the apothecary Mialhe. She made the first application of gr. 0.01 in the morning, then another at the end of the day, and the next morning she put on another centigramme. Hardly half an hour after this she was taken with most serious poisoning, and in a few moments was at the point of death. I arrived about that time and found her in a very alarming condition; she was deathly pale, the pupils were greatly contracted, the somnolence amounted to coma, and she threw up all that was given to her. I thought she would die, but she recovered. As you may well understand, it was important to stop absorption; after having scourged her and administered coffee, I hastened to wash off the little blister, upon which there still remained some morphine.

As I have already stated, you see the advantage of being able to stay the effects of the substance.

This great intensity of action is a disadvantage. But there are others which are only of importance to pusillanimous subjects. For example, all applications on the denuded dermis are painful, no matter whether the substance is soothing or irritating, it is all the same at first. The patient always complains of great pain. Even when you apply morphine upon a blister, the most masculine patient will yell. Women have greater courage. Still more so when other substances are used. The dermis is not intended for contact with irritating substances, while the stomach shows great tolerance, being accustomed to receive a little of everything. There are substances which, in the stomach only cause a slight stinging sensation, but when applied upon the dermis they produce a smarting pain, besides an increased secretion. Thus digitalis on the surface of the dermis may even give rise to small eschars. Those are the disadvantages.

There are also cases in which absorption may fail; this occurs when the application has been made in too much haste, the secretions having carried off the active substance.

In establishing a comparison between the hypodermic and endermic methods, we may say that the slight advantage in favor of the latter consists in the fact that unskilled hands may apply it. If need be, some member of the family may apply the powder. On the contrary, injections require a person possessed of some dexterity and practice in the art, or else the patient must have the courage of administering them to himself—which is rare. Hence it is almost always necessary for the physician to administer the injections himself; this is not always convenient, as he cannot be present all the time. This is the only disadvantage possessed by the hypodermic method, and all that can be claimed over it by the endermic method.

We have now to consider another way of introduction, called the *entodermic method*, which, although not used in a systematic way, may be employed in a certain number of cases. It was inaugurated in 1836 by Lefargue, of Saint Emi-

lion, to whom it was suggested by the practice of vaccination. He concluded that medicamental substances could be introduced by means of a lancet, the same as the vaccine virus. From a therapeutic point of view, the idea was old, for several centuries before him Ælius had recommended the introduction of very active substances under the skin by the aid of some cutting instrument. This is the way Lafargue proceeded: he used a lancet, on the extremity of which he deposited the active substance reduced to a paste, that is, cemented by water or a solution of gum. He stuck the lancet into the region upon which he wanted to act.

Another modification of this process consisted in introducing this same paste in the thickness of the dermis, but also in placing under a watch crystal over the part, a concentrated solution of the active substance; there were thus two ways of introducing the substance. The products inoculated were, in general, alkaloids, for quinine, morphine and atropine were already known, and these were the substances whose use was chiefly recommended. These inoculations were not only applied to produce general effects; they were also used for the purpose of bringing on revulsion, and even the ulceration and the destruction of the affected parts. Thus, for example, those vascular nævi, so frequent in youth, which often disappear and as often increase in size (much to the despair of parents and child), have made physicians seek some way to secure their disappearance. No doubt caustics may be employed, but they are disagreeable, hence more inoffensive, and apparently less alarming means have been tried; among these, vaccination. This is what Lefargue practiced, only, in place of superficial vaccination, the lancet laden with vaccine matter was driven into the arterial or venous tissue.

Inert substances have also been introduced for the purpose of developing an inflammatory process, and even croton oil has been inserted into those tumors.

All these substances produce either a specific or ordinary

inflammation in such tumors, after which a cicatrix takes the place of the nævus.

As I said, Lafargue had the idea of using croton oil as an energetic revulsive agent. Applied upon the skin this oil determines considerable irritation, and produces great effects. He thought its inoculation would determine still more powerful effects, and consequently lead to greater therapeutic results.

That idea has been revived by a Westphalian veterinary surgeon, who has derived from it a process which he applies to all cases; he has even invented an instrument which he calls *a life-awakener* (Lebenwecker.) This instrument consists in a tube containing a spiral spring around a rod bearing at its end needles stuck in a little leaden cushion. After applying the apparatus on the skin, the rod is drawn back, then allowed to spring. The needles, forming a sort of brush, penetrate into the skin, and as they have been dipped in croton oil, they represent so many little inoculations made with a lancet. In this way the oil is carried to a considerable depth, and excites a very decided irritation. But this process certainly does not deserve being ranked as a doctrine, as is being done in Germany.

I now come to the *hypodermic method*, that is, to one of the greatest acquisitions of modern therapeutics. It is the most perfect way by which to insure and measure the effects of medicaments. It is, therefore, the best method, from a practical standpoint, and also for the purpose of interpreting phenomena, because nothing is more important, when conclusions are to be drawn, than to be certain of what has been done. With the stomachic, endermic and respiratory methods, we are never certain of having introduced all that we wanted to introduce, and consequently we cannot measure the phenomena according to their cause. With the hypodermic we can safely do so, because we are sure of what we introduce; the results must be in proportion to what has been introduced, because there is no loss and no destructive causes. We here have convincing elements which exist in no other method; this gives you the extent of its importance.

So far as I know, the first idea of the hypodermic method suggested itself to Fourcroy, the illustrious chemist, who did so much for medical science.

In 1785, he suggested introducing under the skin, in the lamellar tissue (it has changed its name), active substances which would there find all the conditions for integral absorption and the fullest development of all the effects of which they were capable. In support of his theory he pointed to experiments which had already been made upon animals, in whom tepid water, emetics and purgatives had been introduced and followed, in some cases, by their effects. The reason Fourcroy's idea was neglected is, that during his lifetime, and afterwards, the greatest dread existed with regard to introducing active substances into the circulatory system. This fear was not altogether unwarranted, it had some grounds for existence; but this accident happens but once in thousands of injections, hence it should not prevent us from using a method which is the best among all; besides, by observing a few precautions, it is possible to guard against the introduction of substances into the venous system. Anyhow, for a long time active substances have been introduced into the sub-cutaneous cellular tissue, only in a different way from that practiced at present.

There were two processes chiefly used by veterinary surgeons: a wide wound was made into the skin, into which a sharp instrument was introduced for the purpose of cutting the lamels of the cellular tissue, and after an artificial cavity had been formed, the active substances were introduced.

Langenbeck conceived the idea of modifying Lefargue's process, by proposing to insert the lancet below the dermis. Then, by slightly turning the instrument in the wound, allowing the substance to slip in, it was then possible to deposit it in the elements of the sub cutaneous layer.

These were the two processes, to which two others may be joined.

One belonging to Trousseau, which I have frequently seen him use, and which has given some good results. Having ex-

hausted every device for soothing sciatic pains, he one day conceived the idea of introducing sedative substances in close proximity with the point of emergence of the sciatic nerve. For this purpose he practiced a rather wide incision of from 0^m .01 to 0^m .015, and carried it through the whole thickness of the skin to the deep fascia superficialis. He then placed there a large pill containing, among other things, gr. 0.10 extract of belladonna, and as much opium. At that depth dissolution took place slowly; there was a constant supply of narcotic principle, which, in a number of cases, calmed stubborn sciaticas.

He also made use of another process, called *inoculation par enchevillement:* after having made a puncture with the lancet, he followed the section of the skin, and introduced into the cavity thus created, a sort of troche, (similar to a rectal suppository,) which contained a certain proportion of active principle. That formed a kind of wedge—(*cheville.*)

All those processes are barbarous; we now have a much more elegant and far better method.

CHAPTER XIV.

Hypodermic Injections.

HISTORY [continued].—Substances that can be injected.

Injection Syringes.

Alkaloids and Glycosides—Curara.—Mineral salts.—Nutrient substances.—Serum in the blood.—Peptones.

Physical Requirements for Injections—Solubility.—Water.—Alcohol.—Glycerine.

Chemical Requirements for Injections—Effects of acids.—Greater solubility of salts.—Exceptions.

Effects of Alkalies—Correctives.—Albumen.—Hydrobromic acid.

Standards of Solutions—Injections of one-fifth: Ergotine, quinine, quinoidine. Injections of one-tenth: Curara, conin, conicine. Injections of a fiftieth: Morphine, veratrine, strychnine. Injections of a five-hundredth: Atropine, duboisine, daturine, nicotine, eserine and aconitine.

GENTLEMEN:

The era of the hypodermic method begins at that date of 1845–46 when Pravaz, of Lyons, imagined the introduction of a more or less concentrated solution of perchloride of iron in cases of anæurism, so as to cause a coagulation of the blood and thus heal the tumor. It is true that in 1844 an attempt of this kind seems to have been made in Dublin; that is, an endeavor was made to introduce a medicinal substance under the skin. But in reality, it was only in 1853 that the real hypodermic method was invented by Alexander Wood, of Edinburgh.

He made use of Pravaz' syringe to introduce active substances under the skin, and he naturally premised by the use of morphine. He found imitators among a number of progressive men, among others, Charles Hunter, in England; Béhier and Courty, in France, and Von Græfe, in Germany.

At present this method is in general use, and is still growing

in favor, and we should invariably avail ourselves of it whenever we can.

The substances at present used already make up a long list. Morphine was first injected by Alexander Wood; atropine is in constant use as an adjuvant to morphine in determining stupor, or else as an antagonist of that substance; aconitine, of which I was the original user, first, that prepared by Hottot, then Duquesnel's, which is purer; quinine, which has often been injected under the skin, and has been found serviceable, although there are many disadvantages in thus employing it; then again, and without any drawbacks, the hydrobromate of quinine and of cinchonidine; also curara, which Vella, of Turin, employed, as well as Claude Bernard;[1] I have myself used picrotoxine and digitaline; ergotine has recently been exhibited in injections very much as I had used it in 1874, in an affection of the venous system, due to an obliteration of the descending vena cava. At present, we not only can use Bonjean's ergotine, but ergotinine. Some years ago the introduction of mercury under the skin was deemed desirable. Finally, within a recent date, ether, chloroform and emetine have been injected, and I have myself done so, after Dr. Ornella's experiments upon animals. I shall not speak of tartar emetic and croton oil, both of which have been recently mentioned. But as you see, there are at present a great number of substances used. Progress is in the direction of this method, which can but increase in usefulness, especially in nosocomial establishments, where doses may be much more easily repeated than in private practice, which is necessarily disseminated.

I have given you a general indication of the many circumstances in which the method can be resorted to. Let us now look into its details, and first of all, the instrument required. This consists of a syringe, to which different forms have been given. At first, such was the fear of too high doses, that a syringe was invented, the piston-rod of which, in the form of an endless screw, worked in a screw-thread in the cap of the glass

[1] Cl. Bernard. Lessons on the Effects of Toxical and Medicamental Substances. Paris, 1857. Experimental Science, (2d ed.) Paris, 1878.

cylinder. Each half turn represented a drop, and as many half turns were made as there were drops of active substance to be introduced. This was a defective process, and I never would employ it, although at one time no other syringe was sold, either in England or elsewhere. I had Luër make me an ordinary syringe, working by pressure. He only added a sort of gauge on the graduated rod, by the aid of which it is possible to determine in advance when the introduction of the remedy is to stop. This is by far the most preferable way.

When an active liquid is to be introduced by means of the turn-screw, it often happens that one forgets whether half or full turns have been made, hence this is is a frequent cause of error. Besides, when you are obliged to hold the syringe and turn the screw you have to drop your hold of the skin, the needle sometimes comes out, or the liquid is spilled. In fact, difficulties of all kinds attend you.

On the contrary, when the syringe is held in the right hand, between the thumb and medius, the index pressing on the piston, one hand remains free to hold the fold of the skin, and no uneasiness need be felt as to the quantity of active substance introduced. This is evidently the best process, and no one at present uses the old style of syringe.

The substances employed are chiefly alkaloids, and it may be said, in a general way, that the remedies should be the purest active principles of the medicaments in use—the quintessences of Paracelsus. Immediate active principles are divisible into two principal categories: *alkaloids* and *glucosides*. But alkaloids are almost invariably used, even in the case of curara, for, notwithstanding the doubts which have been entertained as to their composition, what appears the active principle in this substance, which I believe to be derived from strychnine, is the methyl and the ethylo-strychnium, for the effects of these last are so very similar to those of curara that they may be considered identical in effects with curara and curarine.

At times, mineral salts are injected. I shall not mention emetine, because, as I previously observed, it is not a real agent

of the hypodermic method; it can only be used as an irritant, and to produce a deep eschar; that is, in the method extolled by Luton.[1]

But we have all the salts of mercury which have been and still are very frequently used by a certain number of practitioners; also, the ethereal liquids, like ether itself, and chloroform, which have but lately been thus introduced. There is also croton oil, which I mention, but which is not to be used; and some have injected alimentary liquids.

Thus, in cases when the stomach is unable to perform digestive labor, or in constrictions of the œsophagus, also in a number of other circumstances, it has been suggested to introduce nutrient substances under the skin. This would not be a way of keeping up strength, nutrition and life, but it would at least enable us to stave off the fatal issue. For this purpose various substances may be introduced, for example, broth, provided it is divested of all fat. But I might as well here tell you that broth is a very delusive aliment; it is more a condiment, capable of exciting the stomach, and it is by an error that it has been classed with peptogenic articles. Milk and the serum of blood can also be thrown in. Peptones might also be injected; that is, substances obtained by the action of pepsine, either upon the fibrinous matter of the blood or on albumen, or on the nitrogenized matter of the muscles. But these peptones would have to be freed from any excess of pepsine, as this ferment would exercise its action just as well on the cellular tissue as upon substances submitted to its digestive effects. Upon the whole, notwithstanding what has been said, no great reliance is to be placed upon hypodermic injections of alimentary substances.

Liquid substances can, of course, be introduced under the skin. This has been done with ether and chloroform. Although these experiments have not been fully successful, yet, in a certain number of cases, sedative effects might be obtained in neuralgias and general pains. But solid substances must be dissolved, and this, as far as practicable, should be done in water. Most of the

[1] Luton. Treatise on Subcutaneous Injections. Paris, 1875.

alkaloids are soluble in water, but unfortunately, in some instances, not sufficiently so, hence the addition of more powerful solvents becomes necessary. Of these I shall only name a few. Alcohol is often used. Chloroform has been recommended, but it is irritating, although later experiments show less of this feature. Glycerine has been employed. It has been used for dividing calomel, and allowing its introduction by the aid of Pravaz's syringe. Mr. Constantin Paul has even suggested the use of glycerine as a general solvent. It is no doubt a good dissolving agent for a great many substances, but it is a polyatomic alcohol, and when used pure or insufficiently diluted it causes an irritation of greater intensity than that which the active substance itself would produce. A solution of creosote has even been proposed. I am really at a loss to say why. Acids and alkaline salts have been used as adjuvant agents with metallic salts. Many of these solvents, such as alcohol and chloroform, are highly irritating, hence they should be used in as small quantities as possible. Injections of distilled water would no doubt be the best, but, as I remarked, there are many substances which, being insoluble in water, have to be made soluble by the addition of substances that are often slightly irritating. As to alcohol, it can be used in rather considerable proportions. Thus, at my outset, in order to obtain a solution of one-sixth in strength of mono-bromhydrate of quinine, I have sometimes used from 2 to 3 parts of alcohol to 10 of vehicle. Even with this relatively considerable proportion, I had no particularly irritating effects, but simply the production of a little heat.

All my students can bear witness that even with this solution of mono-bromhydrate of quinine an intense irritation is never produced in the region where the injection has been given. At most, a little induration is manifested, but usually no trace is even seen of where the injection was made. Therefore, if 3 grammes of alcohol in ten do not produce irritating effects, we should not be over-distrustful as to the topical effects attending these adjuvants of water. However, if much more was added, considerable irritation would follow, and even an eschar might be formed.

Thus eschars have been produced by pure alcohol used in dissolving quinine. It is true this occurred with a cholera patient, who was vomiting everything; unable to obtain a sufficiently concentrated solution in any other way, I used pure alcohol. In this case the tissues were so very dry that the injection produced a small superficial eschar. Alcohol as a dissolving agent is best adapted to alkaloids. This is readily explained by the fact that dissolution is generally effected between proximate substances, while combinations usually take place between dissimilar substances. Alcohol is comparatively a proximate of the alkaloids; besides alkaloids are proximates to fatty substances, and these are soluble in alcohol, therefore it is by alcohol that fatty substances and resinoids may be dissolved.

Acids may be used to facilitate the dissolving of metals, also to increase the solubility of neutral salts, these being less soluble than acid salts. Hence when acid is added to a neutral salt, its solubility is increased. Therefore this is still more the case when acid is added to an oxide or to a metal. As an example, take calomel, which is insoluble. If the protochloride is transformed into a bichloride, the result is a soluble salt. Likewise if you add enough acid to mercury, so as to render it soluble, you can introduce it by the hypodermic method. The same observation applies to a great many organic substances. Strychnine is insoluble, but its salts are soluble; atropine is hardly, while its sulphate is very soluble. The chlorhydrate of morphine is six or eight times more soluble than morphine. Hence, you see, the addition of an acid is a means of promoting solubility.

There are instances, however, where this is not the case. Caffeine, for example, is not any more soluble when in combination, than when free, but this is an exception. Neutral sulphate of quinine is but very slightly soluble, requiring 740 parts of water; hence, it takes 740 grammes of water to dissolve one gramme, while the acid sulphate of quinine is soluble in 11 parts of water. Consequently, bi-sulphate of quinine, obtained by a different process, is always used.

It is generally believed that to obtain bi-sulphate of quinine, it is necessary to add a powerful acid, like sulphuric acid, to the

neutral sulphate. This is not the case; a weak acid will answer as well. It will combine with a portion of the base, and an acid sulphate will be the result, since all of the sulphuric acid will now only be combined with a portion, while, at first, it was united to the whole of the base.

In this way Cl. Bernard was able to obtain a solution of a twelfth by the addition of tartaric acid; citric acid would answer equally well, and increase the solubility of neutral sulphate of quinine in the proportion of 11 to 740.

Alkaline salts, like the chlorides of potassium and iodine, possess the faculty of combining with analogous salts of mercury and copper, and thus forming double salts, in which they occupy the place of bases. Thus with chloride of sodium and proto-chloride of mercury there is formed a proto-chloride of mercury and sodium. These salts, of more complex composition, are far more soluble than the first. Chloride of potassium is therefore added to the salts of the last sections for the purpose of making sub-cutaneous injections with more concentrated solutions.

Besides these adjuvants, we should use *correctives*. In addition to having a good solution, we must bear in mind that active substances are possessed of highly irritating qualities; this is the case with mercurial salts. When even small proportions are introduced, they give rise to little phlegmons and furuncles, and even, in some cases, to gangrene. It would be discouraging if these accidents were of frequent occurrence. Mercurial salts have been combined with albumen. Other albuminoid substances, like gluten and legumine, might be used. To obtain that result, the bi-chloride is added to an albuminous solution. Here we have to note a very interesting chemical peculiarity, because it illustrates how certain substances are incorporated: an albuminate of proto or bi-chloride is formed, according to the salts used, and under this form metallic substances lose almost the whole of their nocent qualities.

These are the corrections chiefly used. Abroad, in Vienna,

for example, these injections are much used. They offer some advantages, hence should be kept in mind.

Quinine has also its corrective. When the alkaloids from cinchona are combined with bromo-hydric acid, they lose all their irritating character. I noticed this immediately some years ago when I first used injections of bromo-hydrate of quinine. Whenever they gave rise to a slight suppuration, it was either because the injection had been given by a novice, who had made a sort of tunnel within the thickness of the dermis, or else because the general sanitary conditions were such that any slight wound would induce suppuration.

That is what happens with tuberculous patients. In certain cases I tried with them injecting bromo-hydrate of quinine for the purpose of reducing their afternoon fever, and that occasionally caused abcesses. But these accidents are rare, and I may say that, among thousands of injections, I have only had five or six cases in which abcesses have formed.

Bromo-hydric acid is not only a corrective of quinine, but likewise of all alkaloids of cinchona. Thus, I have lately made extensive use of injections of bromo-hydrate of cinchonidine, because certain cinchonas from Sumatra and the East Indies, yield a large quantity of this substance.

When the *cinchona succirubra* was first cultivated in those countries, it was discovered to chiefly yield cinchonine; the local physicians found that good results were obtained with it, and being anxious to learn if injections would be harmless, I tried some, and satisfied myself that such was the case. I have at present in my hospital service, a number of patients upon whom no visible traces of injections can be found; all that indicates the places is simply what resembles a flea-bite. I have likewise made injections with what is called *quinetum*. This name has been given to the whole of the alkaloids supplied by the cinchonas grown in the East Indies. We are becoming so poor in cinchona, that we have to make good use of everything. These combined bromo-hydrates are as inoffensive as those of cinchona and of quinine.

I have also made use of what is called *quinoidine*. This is what remains after cinchona bark has been so treated as to extract from it all the crystallizable alkaloids. It is a brownish residuum; I have injected it, and from it I have obtained comparatively good results. No doubt these effects could not be compared with those of the alkaloids as tonics and moderators of fever, but the injections I made were attended with no evil results, although I had but little confidence in the substance used, because of its rather dark color, and the fact that it is not limpid.

This shows that bromo-hydric acid, when in combination, seems to correct those irritating properties which, for a long time, had caused the use of these alkaloids to be abandoned in the hypodermic method. It is indispensable to use only standard solutions; were these made *ad libitum* you would never know the strength of the agent used. There is, moreover, a moral and material obligation in not using more than one syringeful at each time, that is, a dose must be contained within a cubic centimetre. A repetition of the puncture is a repetition of the pain, with a timid subject. Besides, if the treatment is to continue, you would soon no longer find an unpunctured spot on the skin. The syringe is but of small capacity. It only contains a gramme of distilled water; and it is well you should know that all syringes are of the same calibre.

Since the syringe only contains a cubic centimetre of distilled water, it is necessary to introduce into it a sufficiently active dose of medicament; for example, 20 centigrammes of bromohydrate of quinine, or 2 milligrammes of atropine. We distinguish 4 degrees of concentration in the solutions used for injections, and as these standards seem to answer all the requirements, I beg you will bear them in mind.

In the first place, we have very massive solutions, like those of ergotine, of bromo-hydrate of quinine, and of cinchonine, which are made in the proportion of a fifth, because we cannot go beyond that, however desirable it may be, owing to the solubility of those salts. Bonjean's ergotine is soluble in a fifth and even a fourth. A syringeful will contain from 20 to 25 centigrammes.

There are rather less dense solutions of a tenth, like those of curara; no doubt curarine would be desirable, but we have not got it. In these solutions of a tenth, there are 10 centigrammes in a cubic centimetre of water, as in the case of the conin and conicine prepared by Mourrut, which I have injected under the skin without obtaining any great physiological action.

Next come the solutions in most general use—those of a fiftieth; that is, 2 centigrammes in a syringeful of 1 gramme. These are solutions of morphine, veratrine and strychnine; that is, alkaloids that are used by centigrammes, or half centigrammes. These solutions are at present very much used, hence it is well you should remember this standard of a fiftieth.

Use is likewise made of solutions ten times weaker; that is, at a five-hundredth, for substances whose activity is formidable, like atropine, duboisine, daturine and nicotine, which have been in use for a number of years; also eserine, and finally, aconitine, which is the most powerful alkaloid I know of, since its poisonous effects can show themselves with doses of 1½ milligrammes. These solutions can be used in concentrations of a five-hundredth, because you have 2 milligrammes in a syringeful, and it is always easy to divide by eye-measure this capacity into two or four portions. You then have doses of 1 milligramme, or of half a milligramme, of active substance.

CHAPTER XV.

Hypodermic Injections—[*Continued.*]

On the Choice of a Region—Tolerance of certain regions.—Facility for absorption.

Injection loco dolenti—Special regions.

Manner of Operating.

Solution—Its standard; its concentration.—Algæ.—Their effect.

Preventive Methods against the Development of Algæ.

Local Effects of Injections.

GENTLEMEN:

Now that you are acquainted with the instrument, and that you know the standards of the solutions, let us consider the selection of a region.

Several considerations are here to be observed. If our only object is to secure, in the easiest possible way, the absorption of an active substance, from which we only expect generalized effects, we shall choose that region which is most accessible and most absolutely favorable to absorption and its subsequent results.

Guiding ourselves by this absolute statement, we must select a region which is usually covered. With women, injections should never be made in the upper part of the chest. We must choose a region over which the skin is soft, easily separated from the subjacent parts, and in which a fold is readily made; consequently, that region must be underlaid by a somewhat loose and elastic cellular tissue. I do not mean a filamentous tissue, because injections are never successful in such tissues; they give rise to more or less active inflammations, as is the case on the dorsal surface of the hand when it is thin.

The case would be similar with the eye-lids, the scrotum, and regions where the cellular tissue is lax. As far as practicable, we must select regions possessed of considerable vascularity, and not of excessive sensibility. Extended vascularity favors rapid absorption, while excess of sensibility predisposes to inflammatory developments. There are a number of regions which possess all the foregoing conditions. What I have said can be of no interest to those who believe that absorption takes place equally well in all localities, and that selection is simply for the purpose of convenience. Thus there is a foreign physician who believes that a substance can be placed indifferently in all regions. But all careful observers hold an opposite opinion, and this is so well grounded that an attempt has been made to establish a scale of absorbing qualities from the region which absorbs best to that which absorbs least. It has been thus arranged:

1st. The temples and the cheeks.
2d. The hypogastric region.
3d. The front of the thorax.
4th. Supra and sub-clavicular region.
5th. The internal face of the arm and of the thigh.
6th. The nape of the neck.
7th. The external part of the thigh.
8th. The external part of the arm.
9th. The forearm.
10th. The leg.
11th. The foot.
12th. The back.

This distribution would lead us to conclude that the more central the regions the better does absorption take place, and that as we approach the periphery we notice a reduction in the absorbing faculties of the subcutaneous cellular tissue.

I have some reservations to make in regard to this method of graduating the absorbing powers. No precautions seem to have been taken against one of the causes of error most frequently met with. I have reference to the fact that when an injection is made upon a region separated from the skin by but a trifling

space, diffusion may give rise to phenomena which bear the appearance of having been caused by prior absorption and conveyance through the circulation. Let me explain. If you wish to ascertain whether a substance produces tetanic effects upon a frog, you give it a subcutaneous injection, but you must carefully avoid all proximity to the vertebral column, otherwise phenomena will be produced simply through imbibition of the tissue, and a transfer of the substance in contact with the marrow.

Under these conditions, what you obtain with a convulsive agent you would also have with chloroform or chloral and all substances capable of exercising an irritating influence upon the spinal centre.

When I see the temporal region indicated as that which absorbs best of all, the experiments generally having been made with atropine, I am inclined to think that in a number of cases mydriasis was caused more by the diffusion of the active substance than by extra rapid absorption.

Rather subtle distinctions are also made: for example, when we are told that absorption is more rapid on the external face of the thigh than on the external face of the arm, I must say that, although I have made very many experiments, I have never noticed such differences.

I must admit, however, that there are regions which absorb more readily than others, and they are precisely those which correspond with the direction of flexion, and in which vascularization is greater and temperature higher.

My conclusion therefore is, that but few regions possess the desired conditions of great facility for operative mechanism, and a skin which is easily folded—that is to say, superposed over a layer of lax and pliant cellular tissue, besides being a region in which irritability is not very great. The best among these regions are the waist and the abdomen. With these you are almost sure never to have accidents, and you can depend upon integral and rapid absorption.

Another object we should endeavor to secure is the most absolute tolerance for all irritating substances. In fact, there are a

number of medicamental substances which, when introduced into the cellular tissue, are to a certain extent irritating, no matter what precautions may be taken, even if the ingredients are combined with albuminoidal substances. Thus mercurial salts retain their highly irritating qualities in many circumstances, and in spite of all precautions it is impossible to avoid inflammatory nodules, and sometimes even furunculous abcesses. In these cases we must select the most tolerant region, and that is the back, between the two shoulder blades. The skin there easily makes a large fold, and besides, the region is but slightly sensitive. This should always be a guide in the matter of injections. Injections with mercurial salts may be made in this region with hardly any inconveniences.

Therefore, if you only desire facility of absorption and operation you will select the waist. If, on the other hand, highly irritating substances are to be tolerated, you will choose the back.

At times, another object is to be attained. It is desirable to act in a predominant manner over an organ or an apparatus, and for that purpose the active substance is deposited in as close proximity as possible to the region or the organ which is to be modified. But the geometrically shortest road is not always the best. There are circuitous ways which can be taken for the purpose of rapidly and energetically modifying a part. In general, when we desire to allay a pain, we bring the narcotic or stupefactive substance into the neighborhood of the painful region. In cases of sciatica, it is below the gluteal fold that we place the substance, because between it and the nerve the distance is not very great, geometrically speaking. This proves quite successful in those cases. That is a condition we must endeavor to realize whenever we desire to obtain the most extensive possible therapeutic effects upon parts affected either with convulsions or spasms.

But there are other circumstances, as I stated before, in which we can keep far away from the region to be modified, provided the region upon which the remedial application is made is in anatomical connection with the region to be acted upon. For example, when we wish to act upon the heart, we of course know

that it beats in the fifth intercostal space, and under the adjacent parts; it would, therefore, be natural to apply the active substances there. But we must not lose sight of another consideration, which is the vascular connections between the region and the heart itself.

These connections are in the epigastric depression. This has been demonstrated by an army surgeon. It is also in this region that substances should be applied, when intended to act upon the bulb of the aorta, for it has been proven by physiologists that there exists an intimate connection, from a functional point of view, between the epigastric region and the bulb, and that when it is necessary to act upon the bulb, so as to annul its functions, for the purpose of putting an end to syncope, it is there we must address our efforts. If, for example, you are called upon to attend persons laboring under collapse, caused by an excess of chloroform, it is upon that region that you are to bring all revulsives to bear, and chiefly electricity. The same may be said of medicamental substances to be introduced under the skin, for the purpose of acting upon the bulb itself.

Thus, you see, there are cases where, on account of functional relations between distant regions, it is upon the connecting region that medicamental action is to be directed.

But what I have just said supposes the existence of a maximum action more powerful than that upon the whole system, and exerted around the region itself, in which the active substance has been introduced. I shall prove this to be the case. Although a number of able men have supposed that medicaments deposited under the skin act only after absorption, it is, however, evident, from an attentive study of all the facts, that there is considerable topical action, and that the nearer you approach the affected region the more favorable will be the results obtained. No doubt injection is the best method of carrying, with the shortest possible delay, the largest quantity of active principle into the circulation, but from this it does not follow that topical action does not preponderate.

Let us now consider the operative process we must follow in

order to be successful. You must not believe that Wood's little operation is as simple as might be supposed from the instrument, and the apparent absence of obstacles in the way of medicamental substances. There are difficulties with which you must be made acquainted.

In the first place, there are some precautions to be observed prior to the operation; these relate to the *instrument*, the *solution*, and the *subject*. With regard to the instrument, an indispensable precaution is to ascertain each time that the piston closes properly, and that the needle is not stopped up; this will save unpleasant mishaps when you are at work. Besides, each time you practice an operation upon patients liable to impart contagion, you must be careful, as Mr. Pasteur advises, to wash the instrument with alcohol. You know that syphilis is wonderfully well transmitted by vaccination. The fact of this knowledge should put you on your guard against the use of an unwashed needle. Of not less importance is this when you operate upon persons affected with a serious and contaging disease, like diphtheria.

Precautions are to be observed with regard to the solution. The active substance must, of course, be of good quality; I have told you why the solution should be a standard one, and the standard must not be too high. It often happens that, although substances have been well dissolved at the time of their introduction into the liquid which is to serve as their vehicle, yet, on account of its being a saturated solution, crystals are formed after a given time.

In other words, a solution is simply a division into the molecular state, as is the case with the fibrine of the blood serum, or else with the phosphates in the urine, which becomes clouded, because the molecules of phosphates and carbonates, which were in a state of extreme and indivisible division, finally unite and form a molecule which is precipitated, or else floats and forms that prismatic film known by the name of fatty urinal coating.

Something analogous happens in the solutions, especially if they have been prepared at a higher temperature than they after

wards possess. This precipitation has more than one disadvantage. The standard of the solution is reduced, and this does not only take place according to the co-efficient of solubility presented by the active substance at different thermometrical degrees. You might suppose that if at a temperature of $+20°$, it is soluble in the proportion of a tenth, and at $+15°$, of a ninth, that it is one-ninth of the substance which has disappeared and that it is only necessary to filter it. But that is not all. Physicists and chemists know that when a saturated solution has allowed crystals to separate, what remains of the solution is of a lower standard than that indicated by theory. In other words, when crystals are precipitated they carry with them a certain proportion of the substance which should have remained in solution.

Again, there is the danger that a detached crystal may find its way into the syringe; this happened to me once; the crystal stopped up the needle, and as I continued pressing upon the piston, the canula separated from the pump barrel, and all the solution was spilled. Besides, when a crystal has passed through and is introduced under the skin, it acts the part of a thorn, and not only by its mechanical action, but in its capacity as a chemical body, it gives rise to a number of inconveniences which we shall in due time consider.

The solution must be carefully preserved, and in connection with this there are interesting points deserving your attention. After a time all hypodermic solutions become turbid; this is not due to a precipitation of active substance, but to the presence, first of spores, then of simple filaments, which finally ramify and which are formed by a low order of vegetation belonging to the genus *leptomitus*. They are filamentous *algæ*, which might also be called *mucedines;* but the distinction, to my mind, is of but little importance, as I never could see any difference between a *mucedo* and an *alga*. The difference is said to consist in the coloring matters, in the one; but the same plant will show a green color if exposed to light. Thus the *sulpuraria*, of which I spoke, is colorless at the origin of springs, or when it grows

in dark passages, but it assumes a beautiful emerald green when it vegetates in the light. I therefore call them all *algæ*, because they live in water.

These algæ develop in a rapid and, in one sense, destructive manner in all solutions which have stood for some time. They cause the disappearance of a certain quantity of the active substance, and, besides, act the part of foreign bodies. I need not insist upon the inconveniences they thus present, but what I said with regard to crystals applies with still greater force to vegetable substances which are not so easily destroyed. Another circumstance is, that they greatly reduce the strength of the solution to be used. I was the first to call attention to the presence of these algæ in hypodermic solutions; and I advanced the opinion to which I still adhere, that they withdraw a portion of the active substance from the solution, because that substance contains nitrogen, and alga, like all young vegetable cells, requires a nitrogenized substance upon which to develop. Hipp. Bourdon has called attention to another effect of these algæ. As you are aware, filaments and pointed substances form a centre of attraction for all substances that have a tendency to separate from a solution. This is the reason threads are hung in syrup, out of which it is desired to have the candied sugar crystallize. In like manner you may notice that in calcareous regions the radicals of plants which trail in water, are laden with the substances held in solution. Well, the algæ thus developed within solutions intended for injections, produce like effects. You therefore see how objectionable it is to allow the development of this vegetation.

Any of the antizymotics will prevent this development. You know there are a great many antizymotics, and they act in very different ways. We must select those which possess the greatest efficacy and are the least harmful. Mercurial salts are numbered among antizymotics, but you well know why you will not make use of them. You will select something harmless, like borax, to which Mr. Dumas called attention, recommending it as an excellent antizymotic. I explain its effects by saying that it

acts the part of an alkaline body, while these low forms of vegetation require an acid condition for their active development. Dutrochet had already established this, and I have applied that theory to the development of thrush. You may also use hydrolate of eucalyptus, glycerine or bay-cherry water. Of late years, Mr. Lumonsin has advised the use of salicylic acid, whose chief property is its being an antizymotic; that is, capable of delaying very materially the development of all low organic forms. This acid may give good results, but phenic acid, even in the proportion of a one-thousandth, is better, because it is, beyond all comparison, more active. A solution of benzoic acid might be used, as has been done by Messrs. Gosselin and Albert Robin. Vanillin would also give good results. By the use of any of these agents you might delay the development of algæ long enough for you to use up the contents of a phial before they could make any considerable headway.

We now come to the precautions which are to be observed with regard to the individual upon whom the injection is to be made. When you have to administer an injection you must begin by estimating the depth to which you will have to penetrate, because the injection is not to be applied in the cells, and deep-seated areolæ of the dermis, and the adipose cellular tissue that fills it. You have to penetrate, not under the epidermis, as has been stated by a university professor—you can readily imagine that nothing can be introduced under the epidermis—neither within the dermis, as I have told you that this has serious objections, and that such punctures are the cause of most disagreeable accidents, particularly of eschars. You must not operate on the basement layers of the dermis, and in those areolæ which contain more or less globular masses of adipose cellular tissue; this would give rise to eschars, inflammations and deep-seated furuncles. You must penetrate into the subjacent laminated cellular tissue; you must reach the superficial, and even the deep-seated fascia superficialis. This is the reason why I am opposed to the use of the word *hypodermics*, introduced into science by Behier, because it more particularly applies to the

adipose cellular tissue underlying the dermis. It is, therefore, important you should know how deep you have to penetrate. If the patient is spare of flesh, it is evident the distance must be short; but if the person is obese, you will have to introduce the whole needle. You must, therefore, in the first place, make a fold in the skin, so as to ascertain its thickness. You must also make sure that you are not in proximity to any considerable vessel, for it would be unadvisable to open it. If it is a vein, a small quantity of blood might flow out, which would be enough to alarm many persons; besides, you might introduce some of the substance into the vein. Now, I must tell you that there are persons who have been, as it were, struck by lightning by a hypodermic injection, some of the substance of which had been introduced into a vein. This has happened with morphine, among persons who were in the habit of taking it. They always recover, because organic poisons hardly ever kill, unless they prove fatal on the instant. However, it is always unpleasant to see one's patient collapse. This has not only happened to patients, but also to physicians who practiced injections upon themselves. Dr. Chouppe, in a self-administered injection of morphine, having been so unfortunate as to meet with a vein, was overtaken by syncope. For, although absorption takes place rapidly outside of the vessels, it is not, however, so instantaneous as in the present case.

Now that you know the precautions which are to be taken with regard to the instrument, the solutions and the subject, let us examine the manner of operating.

How will you proceed? You must carefully learn this, because many physicians are ignorant how an injection should be given. You make a fold in the skin, taking it up in all its thickness, and it is at the base of this fold, in a parallel line with its direction, that you introduce the needle. You then slowly press upon the piston without letting go the fold you hold with your left hand, and you thus introduce the solution. You will proceed slowly, especially if the quantity of liquid to be injected is rather considerable. The degree of slowness must

be greater and more deliberate in proportion as the cellular tissue is less lax and less lamellated. If the tissue shows some adherence, if the skin is not readily detached, you must proceed with still greater slowness, because, if you inject with any degree of force, either you over distend the lamellæ of the connective tissue, or else you may even happen to tear some of them. You then have rather serious consequences: a plastic exudation and an inflammatory development, which are an obstacle to absorption. In short, without obtaining good results, you meet with disadvantages. It is, therefore, a matter of necessity to impel the injection with great caution.

I have now a remark to make; if you have to deal with a person of dark complexion, young, thin, belonging to southern or semitic races, or simply of Spanish race, you must be on your guard, because you will meet with a stubborn resistance. You must know this, so that you may have the courage to force your way through. On the contrary, when you have to deal with a person of light complexion, having a fresh and rosy skin, like an English woman, the needle then penetrates without difficulty. Penetration is the easier in proportion to the fatness of the subject. This reminds you of what you may notice when endeavoring to break the stem of a plant overflowing with sap: it breaks, when in that condition, very readily; but if it is partially dry, it bends and does not break. Just so when the skin is very much distended, the needle penetrates without any trouble.

What you observe there in the physiological state, you again find in the pathological state. I still have in my hospital service, a patient suffering from a singular nervous affection of the right side of the face and the right arm, accompanied by atrophy of the muscles and hypertrophy of the loose connective tissue. Well, in this distended skin, swollen as it seems with juices, the needle penetrates as by its own weight.

With regard to the local effects, there is at first a stinging, pricking, burning sensation, which occasionally is but little noticeable, but often very painful. Thus injections of aconitine

cannot become of general use, because of the hot and burning sensation they produce; these are so intense that patients prefer keeping their neuralgias rather than submit to an injection.

After a given time the pain subsides, and you observe a small inflammatory areola forming itself around the puncture, and both the skin and the whole course followed by the needle become swollen. In a certain number of cases a real urticaria is even developed. At the same time, there is an exaggeration of sensibility, and if you question persons who know how to observe their own sensation, they will tell you that the mere passing of the finger over the puncture is unpleasant to them. But hardly have two, three or four minutes elapsed, than all these phenomena are reversed, that is, hyperæsthesia is replaced by a deep sedation, by marked reduction of sensibility to pain, and even, in a certain number of cases, by a real absence of pain. This phenomenon is general. It has been noticed by conscientious observers, who only make use of a single remedy. Thus, for example, Dr. Normand,[1] to whom we are indebted for a knowledge of the parasite which is considered as the cause of the Cochin-Chinese diarrhœa, has communicated to me his observation upon the absence of pain caused by hydro-bromate of quinine. It is present, whatever may be the substance used, and what is singular, the same phenomena are observed even when only distilled water has been introduced.

[1] Normand. Memoirs upon Cochin-Chinese Diarrhœa (Archives of Naval Medicine, 1877, Vol. XXVII.)

CHAPTER XVI.

Hypodermic Injections—[*Continued.*]

Common Local Phenomena—Local phenomena which vary with the substances injected.

Diffused General Phenomena—Injections of water.—Phenomena of imbibition, of sympathy of contiguity, and of continuity.

Rapidity of Action of Hypodermic Injections—Their constancy of action.

GENTLEMEN:

We must resume the consideration of the local phenomena, but especially of the secondary phenomena. Whatever may be the nature of the substance used, these phenomena of analgesia are constant. Analgesia is easily recognized; when, at the expiration of a short time after the introduction of a liquid, you examine, with the aid of a pin, the sensibility of a region, you find that, after having evinced a greater sensibility to puncture, (immediately after the injection,) that same region has grown less sensitive. And this insensibility, at times, even extends very far. In order to form a correct idea of this reduction of sensibility to puncture, you must be on your guard against certain causes of error. Comparatively little is known as to the normal distribution of sensibility on the surface of the body. It is not everywhere equal; and if you happen to puncture in the pit of the stomach, you will notice a greater degree of sensibility than in the neighboring regions. The result of this is, that, having made an injection in the upper portion of the right abdominal muscle, if you puncture in the pit of the stomach, you will be led into error by comparing two regions in which sensibility is not the same. Comparison should be established between analogous regions, or, what is still better, with the

homologous region on the opposite side. These are trifling details which, from a practical point of view, have great importance. But the general fact is, that analgesia appears after a few minutes, and, in a number of cases, extends to anæsthesis, properly so called. You can measure this anæsthesis with the aid of a pair of compasses; you will find that a diversion of 12 or 15 millimetres gives rise to a single sensation, while on the homologous region you will obtain a dual sensation. Consequently, you see that it is real anæsthesis which is manifested. In making this experiment, care must be taken to place the two branches of the compasses upon a transverse line with regard to the nervous fibres of the region. For here, again, there are illusions of quite another character which recur in observations upon anæsthesis; if the arms of the compass are placed in the direction of the nervous branches, the sensations will be superposed, and however great the distance, but one sensation is realized; if, on the contrary, the compasses are less opened, but are placed crosswise with regard to the nervous fibres, you will experience two sensations.

These results are obtained upon subjects in good health.

You see how difficult it is to measure sensibility, unless these points are known in advance. Well, a great number of authors who have spoken of sensibility and given its bounds, have bestowed no attention upon these anatomical and physiological peculiarities. We even have *hypothermesthesia*—this is a word I have had occasion to coin for the purpose of expressing the least sensation to cold—for if you make an injection of aconitine, you will observe that even with a bright redness of the region, there is much less sensitiveness to cold than on the adjoining region, although this may be pale.

You see that most of the modes of peripheral cutaneous sensibility can be reduced or extinguished. Well, while this reduction exists, it may sometimes happen that you will observe a painful hyperæsthesia; that is to say, there will be either spontaneous or provoked pain. Thus again, after having made an injection of aconitine, even when the region is in an analgesic,

anæsthetic condition, it may happen, in a number of cases, that you will provoke a very sharp pain by passing the finger over the skin. This pain irradiates along the nervous tracts of the region.

These facts, as you will observe, are extremely remarkable.

When these general phenomena common to all injections have passed away, they are followed by those which are peculiar to the substance used, and which come and conceal the former. According to the nature of the substance introduced, you will have particular phenomena, which will greatly differ. Morphine, and in general, the alkaloids from opium, also ether or chloroform, will give rise to phenomena of stupor, of narcosis, which, according to cases, will cause a reduction of sensibility or a cessation of pain; finally, if they are hypnotics, you will observe that sleep will follow.

Conine always induces phenomena of sedation of the motor system, and these are evidenced either by a reduction of motility, or by a cessation of spasms or convulsions.

Aconitine and veratrine also cause a cessation of pain. Aconitine overcomes all neuralgias of the fifth pair. There is reason to doubt whether it acts in the same way as morphine, hence I place it separately. Quinine and its congeners will determine all the phenomena of sedation which tonics produce. Judging from my own experiments, picrotoxine will act in the same way; so also will strychnine, which exerts its influence upon the marrow. Ergotine brings on an excitation of the smooth fibres. With mercurial salts, or iodide of potassium, resultant antiplastic effects will be obtained.

We now come to an interesting question which is not yet satisfactorily settled in the minds of a number of physicians. Are the particular effects of medicaments generally distributed throughout the whole system, or is there a greater intensity of effect in the region in which the injection has been made? In other words, do substances only act after having been absorbed, or is there, on the contrary, a topical action first excited by them,

and then a development of the general phenomena which they entail?

The question still remains open, but the prevailing opinion, and that which I adopted when I first made my experiments, is that medicaments introduced by injections exhibit a predominance of particular effects in the region itself in which they have been introduced. A number of able men assert the contrary.

Great practical importance attaches to the settlement of this question. If it is believed that substances deposited under the skin must first be absorbed, and then return to act upon the region in which they have been placed, the injection might be made anywhere. This is the conclusion arrived at by those physicians who believe that action is diffused. On the contrary, many, with myself, believe that while there is considerable action in the balance of the organism, the greatest energy is exerted in the region in which the deposit has been made, and in its vicinity. When we desire to act upon a nerve affected with neuralgia, or upon any organ which requires being modified, we are prompted to operate in the neighborhood of and as near as possible to the organ. Hence it becomes indispensable to prove to you that there is a particular and direct action exerted over the region.

The topical actions exerted by hypodermic injections may be divided into two groups. In the first place, those exerted in the very region in which the deposit is made. It seems impossible not to believe that an active substance should determine there more intense local effects than in the rest of the organism. But this is not all. When you deposit a gramme of an active solution within a small space, you can see the effects of this solution spreading afar. And the proof of this diffusion, of this propagation, may be deduced from a number of circumstances which I shall now review.

In the first place, there is a marked rapidity of effect upon neuralgias: for example, when the active substance—let us say morphine—is introduced in close proximity to the affected nerve. In the case of a sciatica of long standing, if you have already

given morphia internally, you will have observed that sedation takes place, let me say, in about an hour; but after introduction under the skin, it shows itself within a few minutes. But, better still, you have only to make this other experiment: In a case of sciatica you inject into the arm 1 or 2 centigrammes of morphine; the following day, the crisis being due at the same hour, you make the same injection, but in proximity to the seat of the sciatic nerve; you will then observe that while the day before it took some time to ease the pain, on the present day the delay is much shorter. The delays should be of equal duration, if sedation was due to the substance having been absorbed and carried into the circulation; but such is not the case.

Cases of double sciatica are rare, but when you happen to meet one you can make the following experiment: Inject one day, in the left thigh, the substance which is to narcotize the sciatic nerves, and you will observe that the left nerve is by far the most influenced; on the contrary, the right one suffers for a longer time, and does not receive the same ease as the other side. The following day do the contrary, and you will have the reverse of the day before. This is very remarkable and demonstrative; consequently, it is impossible not to recognize that there is in this case a direct influence exercised on the region by the substance introduced under the skin.

Some time ago, a careful analysis was made of the modifications of sensibility resulting from the introduction of narcotic substances under the skin, and it was observed that in a considerable region the tactile circle is gradually increased in proportion as the substance penetrates. Thus, immediately after introducing the substance, the region is still quite sensitive, but after some time has elapsed, it becomes necessary to open the branches of the compass in order to obtain sensations.

No substance is better adapted to the analysis of these phenomena than aconitine. When yon introduce half a milligramme of aconitine under the skin, you observe phenomena cf aconitism—that is, all those which aconitine is able to determine; but they are observable in the injected region at an earlier date, and

with greater intensity than in the more distant regions, and it is evident that you have really determined there deeper therapeutical modifications. As you know, aconitine causes a sensation of pricking—something that resembles an itching. When it is introduced under the skin it determines a burning sensation, which, besides, will also manifest itself about the mucous surfaces. But these pricking and burning sensations first exist in the region in which the puncture has been made; they then gain more and more extended regions, spreading themselves according to a course which exactly corresponds with that of the nervous divisions in the region. If, for example, the puncture is made on the leg, the sensations will spread along the course of the fibula, so much so, that those persons who frequent our hospitals, guided by the course of the pain, are able to give an exact description of the anatomical subdivision of the femoro-popliteal regions. They will tell you that the sensation which first existed in the region of the injection, gradually descends. Finally, when diffusion has taken place almost throughout the whole limb, you will again notice this peculiarity: if you happen to rub over a region somewhat distant from the seat of the injection, and one in which modifications can only have been produced through diffusion, you will determine a sort of shooting pain through the nervous branches in connection with those of the region which has been rubbed over. With a dose of only one milligramme, this phenomenon does not present itself in the remainder of the organism. This is a positive proof, added to those already given, that the action of an injected substance is diffused and propagated in diminishing strength as we progress from the seat of the injection.

We must now account for the way in which this propagation takes place, and also explain how it is that a substance introduced under the skin produces a greater effect in the region where it has been placed, than in the other regions of the economy.

In watching what follows a hypodermic injection you will notice that the ridge formed by the solution subsides somewhat rapidly. This is due to two reasons: in the first place, absorp-

tion sets in very early, and then a capillary diffusion takes place in the areolæ of the cellular tissue, which is the more rapid in proportion as these areolæ are wider. Added to this there is a shrinking of the skin and contractile tissues. The result of this is, that the substance which at first only occupied a small space, now covers a wider range, and spreads itself, not only in the subcutaneous cellular tissue, but also through the vascular orifices and along the nervous routes.

There is yet another mode by which these actions are propagated; it is that which, ever since John Hunter, has been designated by the name of *sympathy of continuity and contiguity;* what I explain by the "polarization of the histological elements." The fact is readily illustrated, as far as the muscular system is concerned. In certain morbid cases I have shown that by striking with the tip of the finger upon a muscle, first a knot, then waves are produced, which extend to the extremity of the muscular fibres; the spreading of these waves in this way can only be produced by a propagation of the excitation caused by percussion at a given point. There are no nervous fibres that can account for it.

Finally, transmission takes place by reflex actions, or by others which greatly resemble them. You know that when we excite a certain region, we give rise to excitations in a region in nervous connection with it. I shall mention but a simple example: it is that of the great sympathetic nerve which conveys peripheric excitations into the depths of the parenchymatous organs; thus phenomena of sedation are transmitted in this way from the part that has been calmed, to parts in nervous connection with it.

I called attention some time ago to phenomena of which I have already spoken here, and which I called *echoes*. That is something analogous to reflex actions.

These echoes consist in this: when, for example, there is a pain in the thigh, it is reverberated in the upper portion of the trunk; if a pain is seated at the base of the thorax, it may reverberate as far as the little finger; in short, the pain follows the known course of the cutaneous nerve of the arm.

We do not at present know why these reverberations occur; but you understand, that since they take place with reference to pain, they may also exist with regard to sedation, which would thus be propagated by the agency of echoes. Upon the whole, the important modification, from a physiological and therapeutical point of view, which is determined in a more particular manner than anywhere else, either at the place within which the medicament has been deposited, or within a more or less extended region, may be explained by the three conditions I have just mentioned: first by *imbibition*, then by *sympathy of continuity and contiguity*, and finally by those phenomena of *echo*, which are analogous to reflex phenomena, and to which I have just called your attention.

Among these conditions, *imbibition* is one, by the aid of which we can explain the strange phenomenon of analgesia, which follows after all subcutaneous injections, no matter what may be the substance introduced under the skin. It is really wonderful to think that you may introduce under the skin a substance like strychnine, which excites, or aconitine, which burns, or morphine, which narcotizes, or even pure water, or distilled water, and that in every case, after a given time, analgesia will surely follow, as an invariable result.

To my mind, the governing condition in all these cases seems to be that, whenever a substance is introduced under the skin, whatever may be its nature, *water* is invariably introduced along with it, and that it is the presence of this water in more or less considerable quantities, which at first predominates. This water penetrates as well into the interstices of the connective tissue as into the histological elements, for it is well you should know that these are always more or less laden with water, or, in other words, they are hydrated. They are always very much so among plethoric persons, and with those in whom anæmia has induced dropsies. In other cases they are very dry and thin.

If you compare the histological elements of a healthy region with those of an analogous but inflamed region, you will find that these are more voluminous than the first. This has often

been described; the elements of the cutaneous tissue are greatly swollen when the inflammatory process is considerable, and they then become turbid and granulous. There are, therefore, different degrees of hydration, and it is this hydration which causes a reduction in the several modes of sensibility, and particularly a reduction of sensibility to puncture and to pain.

We may borrow from pathology a point for comparison, by observing what takes place in anasarcous subjects. Wherever anasarca is present, the skin is almost insensible, and sensibility to pain is reduced. But if you explore exactly above the point at which anasarca ceases, you will find that sensibility is unimpaired. The cause of this phenomenon is not due to a general but to a local condition, resulting from an infiltration not only of the cellular tissue, but of the histological elements themselves.

This is the reason why such marked effects of sedation from pain are obtained by simply injecting a syringeful of pure water under the skin.

This fact was first observed in the hospital service of my excellent friend, Dr. Potain, by Mr. Dieulafoy. By a mistake, pure water was injected, and yet the patient affirmed that his pain had been soothed. This is not the idle fancy of an invalid. I have observed numerous cases in which sedation was obtained, but not of so long duration as when sedative substances were used. I had a patient suffering from one of those neuralgias which I call *congestive*—this is one of the cases in which aqueous injections are most successful—who was in the habit of receiving morphine injections. Wishing to avoid his becoming accustomed to these, I gave him an injection of pure water, but left him under the belief it was morphine. The following day he complained that the pain had re-appeared after a time, and that probably the solution had lost its strength. On that day I made him a real injection of morphine, and he was relieved from pain during a long time. Whenever I repeated the water injections he complained of only having had temporary sedation. I have often noted these facts which have been remarked by a great

many observers since Messrs. Potain and Dieulafoy. And recently a work has been published on this subject by Dr. Montecorvo, of Rio de Janeiro.

Sedation lasts as long as hydration does, and when the water has disappeared the pain returns as before. These are therefore only temporary effects.

I have now to speak of diffused or generalized effects. Of course these are similar to those you observe upon the introduction of the same substance by other ways; they only differ from those by the greater rapidity with which they show themselves, by their constancy, and the greater intensity which they present. I shall now review these different peculiarities, and it is important you should fix them in your minds, because they in a great measure constitute the superiority of the hypodermic method.

In certain cases rapidity is wonderful. It is long since Eulenburg's experiments have proven this. It is only inferior to that of medicaments introduced directly into the venous system.

Here is one of these experiments which was made upon a rabbit whose jugular vein was opened, so as the more readily to gather some of its blood. Some amygdaline was injected under the skin of its thigh, and after three minutes, a few drops of blood having been collected, emulsine was added to it, developing a faint odor of bitter almonds. After a lapse of five minutes this odor became very strong. Consequently, in this case, it only required from three to five minutes for a considerable proportion of the active principle to pass into the blood. The experiment was likewise made with yellow prussiate of potash, and it was noticed that while it took fourteen minutes for this substance to first show itself in the urine, when introduced by way of the stomach, it only required five or six when introduced under the skin.

These observations prove that absorption, circulation and elimination have taken place within a delay of three, four or five minutes, since at the expiration of that time the urine shows the presence of a considerable quantity of active principle. Pilocarpine acts even more promptly than those substances. It is an

active principle derived from *pilocarpus pennatifolius*, (rutaceæ,) or jaborandi, according to Dr. Continho. I very often use this alkaloid, in doses of 2 centigrammes, to bring on salivation and sedation in the beginning of an influenza, or during the progress of cardiac affections. At times, pilocarpine shows its effects in an incredibly short period. It has once or twice happened to me that a minute and a half after giving the injection, the face is seen to redden, as if the two sympathetic nerves had been severed. Half a minute later all the phenomena of redness, heat and sweat are in full development; that is to say, that two minutes after the injection the sweat is flowing, and salivation is abundant. I do not say this is invariably the case, because it usually requires five minutes, but I have witnessed the above facts.

This medicament acts with an almost incredible rapidity, which about equals that of medicamental substances introduced by way of the respiratory organs. This rapidity will appear still more surprising when you reflect upon the time required for a full circulation—that is, for a globule to travel through the whole circulatory circle. At first thought, you might suppose that since there are about sixty cardiac propulsions in a minute, the blood must travel in a sixtieth of a minute from the heart to the wrist. But you must remember that the blood globules you feel at the radial are not those which were in the heart at the instant of the systole. Each pulsation of the heart puts in motion the blood-stream which is before it. It is a propagation from proximate to proximate, and not a translation of blood from the heart to the periphery.

Hering's experiments have proven that it requires not less than a minute for a blood globule to perform its circuit. Consequently, for pilocarpine to have acted within two minutes, absorption must have taken place with the greatest rapidity, since that length of time was sufficient for it to circulate and be eliminated by the salivary and sudoriparous glands.

In a vast number of cases that is what forms the great superiority of the hypodermic method, because we often have to act not

only promptly, but we must also introduce into the circulation a considerable quantity of active substance; hence, by this rapidity of introduction you are enabled to act promptly and to introduce a large quantity of active principle.

Another peculiarity deserving of notice is the constancy of effects. Cl. Bernard,[1] by introducing every day 3 milligrammes of curara in the same rabbit, and continuing this experiment for several weeks, invariably obtained the same phenomena within the same time and with the same intensity. After twenty minutes, symptoms of mild curarism would appear, and always last about forty-five minutes. On the other hand, it has been observed that when the same active substance is continuously introduced by any other way, this constancy of results is never obtained. This is due to the fact that in the stomach destructions take place, and absorption is either slow or rapid, and exercised upon the whole or only a fraction of the active substance. There is besides, a question of power and intensity of action which has been observed ever since the method was first brought into use. Those who have studied the effects of quinine have noticed that when introduced under the skin in small quantities, if it chanced not to produce an inflammatory condition, causing an obstacle to absorption, it determined the same physiological and therapeutical effects as quantities four or five times greater given through the stomach.

The difference with atropine is even greater. A centigramme is a toxical dose, but I have had a subject to whom I have given as much as 4 and even 10 milligrammes within the twenty-four hours, which are enormous doses, and yet produced no effects. I began to think he resembled herbivorous animals; but an injection of a milligramme under the skin determined all the phenomena of atropism.

What I observe with regard to atropine, I might repeat as to all medicaments which have been given by the stomach and hypodermically. The advantage is always in favor of the latter method.

[1] Cl. Bernard. "Lessons upon the Effects of Toxical and Medicamental Substances." Paris, 1857.

CHAPTER XVII.

Hypodermic Method—[Continued.]

Different effects of various substances administered through the stomach and by the hypodermic method.—Causes of this difference.

Local accidents attending hypodermic injections.—General accidents.

GENTLEMEN:

It has been estimated that the quantity of sulphate of quinine necessary in an injection is only one-sixth of that required when given by the stomach. All the experiments I have made with hydrobromate of quinine, all those which have been repeated after me by Dr. Normand, confirm this superiority. I have no hesitation in affirming that 40 centigrammes of quinine under the skin—I can now say as much for cinchonidine—give the same results as 1.50 grammes by way of the stomach. Hence, by injecting morning and evening 20 centigrammes of hydrobromate of quinine, paroxysms of fever are averted exactly as if 1.50 gr. or 2 grammes of sulphate of quinine had been taken.

This is a great result, and as it can be obtained without any possible danger to the cellular tissue, there is every reason to make use of it, and adopt it as a method of treatment.

As I stated before, atropine shows even greater differences in doses between the two methods. It may be said that, in general, 3 or 4 milligrammes, by way of the stomach, give the same results as 1 by the hypodermic method. This is in about the same ratio as with sulphate of quinine. With morphine the difference is less, and an injection of 1 centigramme by the hypodermic syringe does not give any more marked phenomena of narcosis than an equivalent quantity of syrup of morphine or laudanum given through the stomach.

But there are cases in which this difference is much greater, or

rather, there are subjects with whom morphine hardly shows any effects by way of the stomach, while it is quite efficient when injected. Consequently *constancy* is one of the fundamental characteristics of the hypodermic method.

There are other substances which it is important to compare according as they are used by either of the two methods of introduction.

Aconitine does not offer any very great differences as to intensity of effect, whether introduced under the skin or given through the digestive organs. But this is providing the stomach is perfectly healthy, and is ready for rapid absorption, all of which conditions are rarely met with. Otherwise, if the stomach is in a saburral condition, if it still contains alimentary residuums and all the ferments accompanying them, when aconitine is introduced, it will produce no effects. I have seen persons who have taken milligrammes of the best aconitine, and who have hardly felt any of its effects, because it is an unstable substance, which is easily destroyed by any of the chemical bodies, and especially by ferments. But in a healthy stomach the difference is not very great; it is as one to two. That is to say, if 1 milligramme of aconitine is required, when given internally, to produce marked physiological effects corresponding with the therapeutic wants, only half of that quantity is necessary when introduced under the skin. This difference is not without its value, but it is not as great as in the case of quinine.

On the other hand, ergotine, when it is introduced by the hypodermic method, would seem to offer the other extreme. The substance here mentioned is not the alkaloid from ergot; that is not as yet to a certainty known; but it is a more or less concentrated extract which represents the principles and action of ergot, not intensified, but rather reduced. We have Bonjean's ergotine, which is an alcoholic extract of ergot; we also have a more concentrated extract, lately prepared by Mr. Yvon. Yvon's extract, which is a light topaz-tinted liquor, is so concentrated, that one gramme is equivalent to one gramme of ergot, while Mr. Bonjean's somewhat dense extract is much inferior to

ergot itself. My own experiments have satisfied me, that to produce the same therapeutic effects, it is necessary to use no less than five times as much of it as of ergot.

But this solution of ergotine has the advantage that it can be made into a lotion and injected under the skin. Recent experiments seem to indicate wonderful differences between the hypodermic and stomachic effects of this substance. It would appear that by introducing 10 or 15 centigrammes of Bonjean's ergotine, a hemorrhage is stopped the same as by giving gramme 1.50 of powdered ergot.

I have reason to think these are exaggerations. For my part, I have never seen any effects from ergotine injections indicating such intensity of action. I have observed effects, but I never injected less than 25 centigrammes at a time. In certain cases I have seen an hemorrhage stopped; but if we are to believe the recent observations communicated to the Therapeutic Society a few months ago, a difference of forty-fold separates the action of these injections from that of ergot itself. In fact, it is claimed that an injection of 10 or 15 centigrammes of ergotine produces as much effect as 4 grammes of ergot. I cannot admit this. I very much fear, that by mistake a causal relation has been thought to exist between the introduction of the substance and the discontinuance of the hemorrhage, while, in reality, there was nothing more than coincidence and spontaneous cessation.

However this may be, it is indispensable you should understand why these differences are possible, and why such great divergences can exist in the intensity of action of certain substances when introduced under the skin, or given through the stomach.

In the first place, it is important to know whether the substance is destructible or not in the primæ viæ. It is evident, that if a resisting substance is introduced into the stomach, it will finally be absorbed. Absorption will take place more slowly through the skin, but still it will take place, and a time will come when, having reached the parenchyma in a sufficient quan-

tity, it will determine all the effects of which it is capable. In this case there is no difference between the two methods.

There is another circumstance, which is the greater or less degree of adhesiveness of the substance introduced to the areolæ of the cellular tissue and to the organs in the midst of which it spreads. This adhesiveness is real.

In the case of aconitine, I have called your attention to the great intensity and endurance of its local effects. Not only does it cause a sharp, burning sensation and shooting pains, but those effects continue, at times, for two hours. I have seen subjects continue a whole afternoon in the agony caused by aconitine introduced under the skin. This proves its local adhesion, and this adhesion must have its importance, because as the substance is not carried away like some others by the circulation, its effects are not distributed through the whole system.

There is a third reason for the difference in the intensity of effects between substances introduced under the skin and those given through the digestive organs. These effects may depend on the system over which their action is exerted. If the medicaments or poisons exercise their action directly through the blood, and on the blood itself, it is evident that if they penetrate in large quantities at a time, that action will be violent, fulminant, instantaneous. On the contrary, if substances exert their influence on the nervous centres, and if this influence is only exerted by the penetration of those substances into the elements of the nervous system through a sort of temporary combination with these elements, a considerable time is required for this to take place, and although you may introduce into the circulation a large quantity of active substance capable of producing effects on the nervous system, these effects always requiring a certain time in order to be produced, there will be no great advantage in introducing substances hypodermically rather than through the stomach, because if they are not destroyed they will be absorbed with sufficient rapidity to penetrate into the circulation and thence into the parenchyma.

Now those combinations between the substances and the

elements exist. A certain number of perceptible modifications have already been observed in the histological elements of the nervous system, when these have been impregnated with an enormous quantity of toxical principles. These experiments have not as yet been fully carried out, although the first of them dates back some ten or twelve years.

They open up a new path and enable us to understand what was already indicated by inductive considerations, that substances probably penetrate into the histological elements.

I shall give you a few examples. Let us suppose that you rapidly introduce into the blood phosphorus, oxide of carbon, nitrite of amyl, anæsthetics—in fact, any of those substances which act directly on the blood. They will act, producing what we might term lightning strokes. If you happen to introduce them by the subcutaneous method, and they come into the circulation in large masses, they will produce effects nearly as violent as by inhalation. And there will here be the widest difference between the effects produced hypodermically or by way of the stomach. If, on the contrary, you introduce substances which, like morphine, act on the nervous centres, there will be less marked differences, because these substances have to penetrate into the histological elements, and for that purpose they require a certain time.

I must now point out to you a few applications of these principles. I stated that we could in that way understand why certain substances act almost as well through the digestive organs as by injection, and how with others the contrary is the case.

Take, for example, morphine. This is very stable, and also it requires considerable time to penetrate into the histological elements of the nervous system. These two conditions favor its introduction through the stomach.

Quinine has not the same qualities. It is destroyed; in the literal sense of the word, *destruere*—to lose structure. It readily changes into quinidine and quinicine; the former is almost without effect; the latter has none at all. Therefore, quinine, when in the stomach, without disappearing, (you might take up the contents of the stomachic retort and still find the alkaloid,) may

become that residuum which is traced in the urine. For when a gramme of sulphate of quinine has been introduced into the circulation you recover in the urine 85 centigrammes of an alkaloid, isomeric with quinine; this is quinidine or quinicine. It is this species of destruction which prevents quinine from acting quite so well when given through the stomach as when introduced under the skin. It has to penetrate into the elements of the nervous tissue, but when introduced in the stomach it is less resistant than the alkaloids from opium; hence there is a difference as between one and five, when the effects of the two methods of introduction are compared.

Before passing judgment on the value of the hypodermic method, let me say a word on the *local accidents* attending injections.

These may be divided into actual traumatic accidents and ulterior accidents due to the peculiar activity of the substances used.

The first of all accidents, and that which most frequently happens, is a quick, sharp, agonizing pain produced in a more or less circumscribed region, and caused by the needle having come in contact with a nerve fibre. This is of no consequence, and the pain is not lasting.

Another accident which, in certain cases, may assume more gravity, is when the needle penetrates into a vessel of some magnitude. Two secondary accidents may result from this. Either you cause a slight hemorrhage, which greatly alarms timid subjects, perhaps an internal hemorrhage—a kind of small thrombus which leaves an ecchymosis—or else in a number of cases there happens the serious accident I spoke of in the last lesson, and which strikes with a sort of sideration the subject in whose venous system the substance has been directly introduced. You may then witness an affecting scene: loss of consciousness, attended by deathly pallor, coma, and stertorous breathing. Something really fearful. However, it is very seldom that these accidents prove fatal, unless you happen to meet with a person affected with organic disease of the heart.

There is also another slight accident which may worry you if you do not know of it; it is an emphysema localized around the puncture, and which at times assumes considerable importance. It has two origins, and may arise with all sorts of substances; it may be due to the fact that you are at fault in not having fully expelled all the air from the syringe, and that some of it has been introduced into the cellular tissue. This is of no consequence. But since hypodermic injections of chloroform have been made, a more persistent and larger emphysema has been noticed around the puncture. A crepitation is almost immediately observable, similar to that attending an emphysema due to anthrax, or to a pulmonary rupture. The cause of that emphysema is unknown, but I believe it may be due to a volatilization of the chloroform, which, although less volatile than ether, has still considerable vapor tension at 37°. Anyhow, these emphysemata appear unimportant.

Let us now consider the ulterior accidents. In the first place, there is an exaggeration of all the physiological effects due to substances introduced under the skin; these, as I just now stated, are capable of producing considerable effects in the locality in which they are injected. Hence, if you do not proportion the doses, you may determine toxical in place of therapeutic effects.

Finally, we have the effects due to the introduction of these same substances into a vein. These phenomena are unexpected; the others may be foreseen, hence forestalled, by using moderate doses. When introduction into the vein takes place, you observe all the serious phenomena I have spoken of, and the case is embarrassing.

I shall tell you how to guard against these accidents. But I have first to mention certain initiative troubles resulting from excess of sensibility, and caused by the substances introduced under the skin. These are an exaggeration of the normal troubles. I told you the patient always experiences a slight flush of heat, a smarting pain, and usually exhibits a sort of erythema. When the phenomena are limited to this, and even

to an eruption of urticaria, they have no great importance. But these irritative phenomena may assume more gravity. When the inflammation gives rise to an inflammatory node, it becomes a serious matter. This node seems due to two circumstances; in the first place, to the nature of the substance; for example, it would seem, that picrotoxine produces larger exsudats than any other substance. In the case of a woman whom I attended for a labio-glosso-pharyngeal paralysis, and with whom I had obtained considerable success, since she grew worse each time I discontinued the injections, after some fifteen injections I noticed that her arms appeared like bags filled with filberts. I have had occasion to observe this in another case, but I do not hold it to be a general rule.

The other circumstance is that these nodes are produced by the presence of irritating corpuscles in the substance inserted under the skin. In giving an injection, you must examine the solution very carefully, because the least particle of mineral or organic substance, or of an alga, which develops so easily, is usually sufficient to bring on a persistent sub-inflammatory development. And at times, after two or three weeks, you still find nodes under the skin. These are the two principal circumstances in which these nodes are produced. But this is, as yet, of only minor importance.

In certain cases, matters become more serious, and you will notice around the puncture not only an inflammatory node, but a more or less wide œdemato-phlegmonous puffiness, which alarms the patient, and should alarm you, because suppuration might set in.

This is a real accident, important in itself, and besides, if you have to repeat the injections on the patient, a multiplicity of such abscesses would finally induce traumatic fever, and prevent you from continuing the treatment. These accidents are of frequent occurrence with certain substances, like mercurial salts, or sulphate of quinine, but we need no longer mention this latter, since the bromo-hydrate secures us against this danger. Besides this, there is a fifth degree, during which a gangrenous blotch

is formed. I do not mean those blotches due to the introduction of the substance into the dermis, but the sphacelus following the inflammatory development, and complicating it, by suppressing all sources of irrigation for the skin and subcutaneous cellular tissue. This sphacelus has the double inconvenience of being very disagreeable at the time, and of leaving real cicatrices or indelible maculations.

There is no necessary connection between the various affections and the different accidents which may be determined by substances introduced under the skin. There are substances which cause violent pain and never any inflammation, while others awaken no sensitiveness, but produce nodes; finally, there are some which occasion no pain, but give rise to suppuration. Picrotoxine, for example, is not felt, but always produces a node. On the contrary, aconitine causes such agonizing pain, that patients, though relieved of their neuralgias, prefer not using the remedy; but it never causes inflammations, unless some algæ have been introduced under the skin. Therefore, pain and inflammation are not always present together.

I have shown you the different results caused by the nature of the substance used; the differences are equally great according to the subject receiving the injection. There are subjects with whom hemorrhages very readily take place; it is those who have a hemorrhagic diathesis. But diathesis is not indispensable; if there exist, in certain regions, conditions analogous to those of scurvy, the same hemorrhagic phenomena will be produced. For example, when injections are made in limbs which have been long stricken with immobility, and are affected with what Mr. Cloquet has designated under the name of *local scurvy*, the punctures will give rise to slight hemorrhages. What exists there under the influence of a traumatism, which has made immobility compulsory, likewise happens in spontaneous diseases.

I have, at present, at the Hospital Beaujon, a patient who is affected with a trophoneurosis of the superior right half of the body. He has pains, and, at the same time, shows phenomena of muscular atrophy. But while the important organs, those

which, like the muscles, have a peculiar structure, are being atrophied, the cellular tissue, which is only an organ for filling up, is increasing in thickness. Hence, wherever the muscles have disappeared, this man shows a very thick subcutaneous adipose tissue.

Well, I cannot get the needle to penetrate through this region without bringing on a hemorrhage.

There are subjects who are also exposed to all the inflammatory accidents I have described, and to such serious lesions as gangrenous phlegmons. This happens among those whose general sanitary conditions are bad, and among those who suffer from one of those diatheses, which cause important modifications in nutrition, or those who have reached the ultimate period in a chronic disease, with hectic fever. Thus, among tuberculous patients who have reached the last period among those under the effects, and of typhoid fever, in puerperal affections, in which suppuration so readily takes hold of any little traumatism, even that caused by an injection; likewise in cases of albuminous and saccharine diabetes; in all those cases suppuration very readily sets in. The practical lesson to be drawn from these considerations is that medicaments should not be introduced by the hypodermic method in subjects who are in such precarious conditions, because the effects will not be satisfactory; besides, you might easily appear to have harmed them, when your object was their relief.

I turn back to general accidents, which, as I stated, consist in the penetration of active substances into the circulatory system. This is what must be done in order, as far as is possible, to prevent these accidents: you must, of course, carefully explore the region upon which you are about making an injection, so as to avoid all bluish lines: you will likewise avoid the large venous trunks, which anatomy has taught you to know. The needle must also be directed parallel to the general direction of the veins in the region; in general, this direction is also that of the axis of the limb. You must also direct the needle from the centre towards the periphery; that is, from the upper articulation of the limb towards its extremity. If the needle is thus guided,

should you be so unfortunate as to enter into a vein, absorption is never so rapid as when the injection is impelled in the direction of the blood current. To this might be added the precaution recommended by Béhier: this consists in introducing the needle alone, when, if no blood appears, the injection is proceeded with. This process, however, does not afford implicit guarantees, because it may give rise to false alarm should there be a show of blood, due to the conditions of the cellular tissue. It may also inspire unwarranted security, from the fact that if the needle is introduced along the course of a vein, there being no pressure exercised in a retrograde direction, there may be no refluence in the interior of the canula; and even if there should be, the canula may be so small as to prevent an escape of blood.

CHAPTER XVIII.

Hypodermic Method [*Concluded.*]—*Acupuncture.* —*Transfusion.*

Substances for which the hypodermic method is unfitted.—Objections to the method; its advantages preponderate.

ACUPUNCTURE: Electro-puncture, parenchymatous, or substitutive method of injections.—Theory of, and criticism on, substitution.

Introduction of medicaments through the vascular system. History of transfusion.—Principles.

GENTLEMEN:

Besides the objections attending hypodermic injections, we must admit this method does not always possess the superiority claimed for it over other ways of introduction. For example, there are subjects—the case is a rare one, but I must notice it—who are about as sensitive to a substance like atropine, when introduced in doses of one or two milligrammes into the digestive organs, as when introduced into the subcutaneous cellular tissue.

There are other objections to this method: for example, nitrate of potash, cod-liver oil, and all other substances requiring considerable doses in order to act, cannot be introduced, because the quantities would be beyond the capacities of the cellular tissue. This also applies to alimentary substances, which could only be introduced in such minute quantities as to have no perceptible effects.

Medicaments, such as oily bodies, which are not of themselves soluble, will not find, in the cellular tissue, the necessary elements to effect their dissolution. There are other substances which can only be dissolved by the aid of acids; oxide of zinc is soluble in hydrochloric or sulphuric acids; and the chlorides of zinc are irritating and caustic substances, which, consequently, cannot be

introduced under the skin. There are other substances which are directly soluble, but very irritating, like phenic acid, creosote and perchloride of iron. These cannot be introduced by the hypodermic method, because they would cause phlegmons.

There are again substances which cannot be thus introduced by the subcutaneous method, because they should be taken with the food. Such are those which either become soluble during the digestive process, or require being mixed with the chymous mass so as to come into the circulation with the aliments themselves; these are the medicaments which have been named *eutrophics*, which I have called *histogenics*, that is, which help in forming histological elements, for instance, the calcareous phosphates, cod-liver oil, and even iron, which is likewise an aliment properly so called. Alteratives, like certain arsenical preparations, should be taken at meal-time. This hour has also been recommended for taking preparations of phosphorus, because they are better assimilated under those conditions.

Finally, when you desire to exert a topical action upon some mucous membrane, as that of the respiratory, or especially of the digestive organs, you will certainly give your preference to introduction by inhalation in the first case, and through the stomach in the second. And here there is a peculiarity which is interesting to know.

There are two kinds of emetics, as I have long ago established, and as I again recently stated before the Academy of Medicine. There are emetics which act on the periphery, on the distal extremities of the nerves of the stomach, and the par vagum, or else on the nervous extremities of the branches of the solar plexus; but there are others which, on the contrary, act on the bulb. The first act after the manner of an indigestion; the second like a meningitis. Apomorphine is the type of this last category of emetics. According to all experiments, it seems to act upon the central nervous system while exerting its influence upon the bulb.

But the majority of other emetics, tartar emetic itself, and especially the emetics derived from the vegetable kingdom, act

directly on the stomachic and intestinal mucous membranes. These last, as also ipecac, and all plants of an emetic character, seem to act directly on the gastro-intestinal mucous membrane. The proof of this is easily given: When emetine is introduced hypodermically, it requires 20 to 30 centigrammes to produce effects, which are longer in appearing and less intense than those obtained by a smaller dose given through the stomach. And what is curious, when this experiment is made upon animals, and they are killed, the emetine is found in the digestive tube. This shows that when introduced into the cellular tissue, it had first to be absorbed, then circulate and be brought by the arterial blood into contact with the organs it excites when given through the digestive apparatus; and it is only after having been secreted in sufficient quantities in the digestive tube that it commences to produce its effects. Therefore, it is best not to use the hypodermic method when you desire to bring on vomiting or nausea.

Among the inconveniences attending the hypodermic method, I may add, that its application generally requires the physician's intervention. In the majority of cases, neither patient nor attendants can be entrusted with the performance of the operation without assuming undue risks of accidents.

In conclusion, I may say that the hypodermic method distinguishes itself from all or nearly all others, by qualities of such striking importance, that in a majority of cases they overbalance all disadvantages which the method may otherwise present. It offers us rapidity of action, constancy, and great intensity and absolute security as far as physiological and therapeutic effects are concerned, since we are certain that all we wish to introduce has been introduced. Besides, by the aid of exact doses we arrive at a degree of preciseness which it is impossible to attain in any other way. Upon the whole, it is really a scientific method, and one which should always be resorted to when applicable. Recourse should be had to it when the effects of different substances are to be measured, and it is, thanks to it, that such precise and conclusive results have been arrived at, as

those obtained by Frazer, in England, with the principal alkaloids and their reciprocal actions.

I have now to mention another method of introduction—that through the deep cellular tissue, the deep-seated organs, and the lymphatic ganglions. This method of introduction into the very depth of organs has, of late, attracted attention, but, notwithstanding, is not of recent date.

Some fifty years ago *acupuncture* was borrowed from the extreme east and introduced into medicine; electricity was subsequently added to it, and this formed *electro-puncture*. I remember when this method was still in favor; I have inserted platinum needles in the thighs of persons complaining of sciatica, and I have done so under the direction of my illustrious teacher, Lallemand, of Montpellier. Mr. Julius Cloquet wrote a book,[1] setting forth the merits of this method, not only according to the reports of foreign physicians, but also from observations made by himself.

About that period Fabrê, knowing certain facts connected with electricity, conceived the idea of applying it for the purpose of introducing active substances into the deep structures of a limb. A platinum needle is passed into the structure deep enough to reach the desired spot, and placed in communication with a battery containing a solution, say of sulphate of copper. If the needle is connected with the negative pole, that pole will transport the electro-positive substances attracted to it; the substance and its effects will therefore be carried into the depths of the limb. On the contrary, if the connection is made with the positive pole, the reverse will take place—the substances composing the solution, and acting the part of electro-negative bodies, will be transported and attracted to the positive pole. We shall, therefore, find on that side, for example, iodine, chlorine, arsenic and phosphorus.

Fabré applied this method in cases requiring the resolution of chronic congestions, and in some instances met with good results.

The method is now quite abandoned, yet there are cases in

[1] Cloquet. A Treatise on Acupuncture. Paris, 1826. 1 Vol. 8vo.

which it might perhaps be utilized. For example, to destroy uterine myomata, substances might thus be introduced into them capable of bringing about their necrosis. The method was given up on account of its difficult application, and also because the current did not always transport active substances. We now have improvements over the former instrumental appliances which might remedy these defects. Of late years that method has been replaced by another, which is allied to *hypodermic injections* in so far that a somewhat enlarged Pravaz syringe is used with it. Its author, my former disciple, Professor Lutton,[1] of Rheims, having to deal with a number of cases refractory to ordinary processes, as for example, those enormous lymphatic ganglions of the neck which extend into the interior of the thoracic cavity, and against which everything fails, thought the patient might be relieved if by some process those tumors were, if not removed, at least dissolved.

For this purpose, he introduces a canula, or a slender exploring trocar, into the tissue to be modified. He then watches the fluid evacuated, and according to its nature, decides whether or not it is advisable to apply the injection which is to modify the diseased organ, either by producing a more or less violent inflammation, or by simply determining changes in its sensibility or its nutrition. Strictly speaking, this method hardly comes within the limits of my subject, because it has not as an object the introduction into the circulation of substances intended to produce diffused effects. Nevertheless, as, in a number of cases, the substance does penetrate into the general economy, and as this method is a sort of annex to the hypodermic one, I deem it advisable you should be made acquainted with it.

Phenomena of irritation, even of more or less advanced phlogosis, with suppuration and sometimes gangrene, are liable to follow. Alcohol, more or less concentrated tincture of iodine, bichloride of mercury and nitrate of silver are chiefly used. Dr.

[1] Lutton. A Treatise on Subcutaneous Injections for the Purpose of Producing Local Effects. Paris, 1875.

Lutton seems inclined to attribute all the effects attending these different substances to *substitution.*

I never forego an opportunity of condemning this expression, because it is not scientific and has been the cause of great confusion.

Trousseau called this process of substitution a *homœopathic action.* The homœopathists took advantage of this, and always mention Trousseau as having been one of their number. Vainly did he protest, claiming only to have said that it was but another inflammation replacing the first, and carrying away the first irritation by the aid of a greater excitement. I will show you that that expression was doubly unfortunate, since it did not even define a scientific idea.

For example, chloride of sodium is injected into a region in which there exists a pain, and they say chloride of sodium produces a sharp pain which is substituted for the former one. This is all wrong; they should say chloride of sodium causes a very rapid irritation, and by means of this, which is not lasting, a sort of nervous exhaustion takes place, exactly as is the case with persons suffering from shock after accidents. It is what Dupuytren termed a *nervous bleeding.* But the pain which momentarily disappeared soon returns.

Tincture of iodine resolves congestions; it is the substitution of an acute for a chronic inflammation. Of course, an inflammation has been excited; but is this all? Iodine, in small quantities, acts as a resolvent; and in large quantities, as an inflammatory agent. Either of these effects may have contributed to the disappearance of the tumor. But that is no *substitution.* With nitrate of silver it is the same; it substitutes nothing, but it produces an eschar in the depths of the organs in which it is deposited, and this eschar is eliminated through the process of suppuration. A similar process has been long in use. By the aid of a red-hot iron, or by means of a cautery, purulent issues and consecutive resolutions have been determined; consequently, as you see, there is no occasion for using the word *substitution* in cases pertaining to this method.

The professor from Rheims, who has advocated these injections, had been anticipated. I will not speak of Nelaton, who introduced a few drops of alcohol into furuncles for the purpose of aborting them. This rather belongs to the *entodermic* method; but Jobert de Lamballe has already suggested the introduction of a few drops of tincture of iodine into the epididymis when congested. Injections in the serous cavities, as in the vaginal folds, may be added to the above examples of antecedence to Lutton. Still, we must give to the professor from Rheims the credit he deserves. He has gathered all these facts into a general method, and in a number of cases has obtained interesting results. It is true that in others they have been null or regretable, and as a rule illusive.

Parenchymatous injections have been used in cases of obstinate neuralgias, and especially against sciatica. We tremble, *a priori*, at the idea of introducing in close proximity to the sciatic nerve, at least when impaired in its functions, such substances as a concentrated solution of nitrate of silver, capable, as it is, of producing a phlegmonous inflammation. No doubt nitrate of silver and the other more or less caustic substances introduced by Lutton and others, have caused suppurative phenomena in the deep-seated cellular regions, but fortunately the course of the needle itself has supplied an outlet for those products of inflammation. When this course has become closed, accidents have happened; but it usually remains open, because in withdrawing the instrument there are always a few drops of the caustic solution which remain in its path. In this case, after a few days, more or less serous or purulent secretions are evacuated without causing any great damage to the nerve in whose proximity the inflammation is seated. It is, thanks to this circumstance, that more serious accidents do not often happen. At all events, I have placed you on your guard against illusions which have been indulged in by able men. The relief is but momentary; after a short time the neuralgia returns the same as ever. I have had occasion to witness this in the case of one of the most eminent men in the medical profession who, against my advice, insisted

upon having injections of nitrate of silver made upon himself. They produced abscesses, but absolutely no advantage from a therapeutic point of view.

I have now reached the last among the avenues of introduction. It is that through the vascular system, and particularly through the veins, as being the least dangerous method.

This method of introduction is already over two centuries old, the first injection in the veins having been made in 1665. There are even traces of much older instances than this. Verses from Ovid seem to indicate that he knew of the practice, or believed in the possibility of intravenous injections, and particularly of *transfusions of blood,* for he says: [1] "Take from me this old cruor, that I may fill my emptied veins with youthful blood."

Probably this is nothing more than a poetic image, but there is an instance which seems more authentic, and which takes us back nearly four centuries. It is the case of Innocent VIII., who having fallen into a state of marasmus, called in a Jewish physician, who conceived the idea of transfusing blood into his veins. The blood was procured from three little boys, who died, probably because too much was taken from them. This operation took place in 1492, the year in which America was discovered. The operation did not save Innocent VIII. from death, and lost the three children, so the Jewish doctor was obliged to flee for his life.

It is also said that in 1615 Libavius, whose name is celebrated in chemistry, practiced transfusion, but this is not certain.

In 1665, a really scientific period commenced at Oxford, where the idea was first had of infusing medicaments in the veins of animals. That proposal was made to the Bishop of Exeter, who adopted it; we must suppose that at that time bishops were not members of the society for the protection of animals. This gave rise to the idea that medicaments, and blood even, could be injected into the human veins, and is the starting point of the method as known to us at the present day.

[1] "Ut repleam vacuas juvenile sanguine venas." Ovid, Metamorphosis. Lib. VII.

In 1665 Lower practiced the first transfusion of blood. He was closely followed by Kaufmann, in Germany. At one time, judging from the results announced, it seemed as if the secret of perpetual youth had been discovered. But a number of accidents happened, and the Parliament of Paris passed a resolution surrounding this operation with a number of guaranties, which were a credit for the doctors of that period; it was necessary to be a doctor of the faculty of Paris in order to have the right of practicing it. But the operation soon fell into disuse, and it was only in 1818 that it again re-appeared.

It was applied to animals by Messrs. Prevost and Dumas, and by Magendi, in 1823. Since then numerous transfusions have been made. I shall first speak of these, and will then dwell on medicamental infusions.

What fluid should be injected? Everything has been tried—serum, globules and more or less well-dissolved hemoglobine. Trials have been made with natural blood, and with blood nearly so, but stripped of its fibrine. We shall review these different ways of effecting transfusion, and judge their results.

Let us begin with serum; it only gives illusive or harmful results. At first sight, it would seem advantageous to introduce it, since it is an aliment, containing albumen in considerable proportion, fibrine, and all the salts naturally contained in the blood. But in Prevost's and Dumas' experiments, serum has never given any results—it has never prevented animals from dying—and Dieffenbach's experiments confirm theirs. Moreover, it is harmful. It has been observed that 300 grammes of serum introduced into a dog produce nervous convulsive phenomena, a sort of delirious agitation, followed by collapse and death in twenty-four hours.

The conclusion, therefore, is that if any benefits are to be derived from the transfusion of blood, we must not have recourse to serum.

Hemoglobine has been injected without producing any good results. I may even say it is harmful, in proportion to the

quantity in which it is introduced. Mr. Paul Bert[1] considers hemoglobine, when alone, more as a poison than as an agent of respiration.

As to the globules, it is evident that if they could be introduced one at a time, without any difficulty, they would produce considerable activity in the great functions. But they have to be introduced by the aid of liquid substances. Must this liquid be the serum, or is it advisable to deprive it of part of its elements, and of the fibrine in particular?

Let us first settle a previous question. Blood should be introduced in its complete state, or nearly so, but it must be liquid. You know that blood coagulates; therefore, what is the best way of keeping it in a fluid state?

These ways are numerous. In the first place, it has been observed that a low temperature keeps blood in a fluid state for a long time; Dieffenbach mentions three hours when in a refrigerant mixture. Unfortunately this iced blood cannot be introduced in the veins without the most deplorable consequences. Therefore, our only recourse is to receive the blood in vessels heated to a temperature of $+ 37°$ or $+ 38°$, which is nearly that of the animal supplying it. By this process blood remains fluid for about forty-five minutes; this gives ample time to inject it, especially if a given quantity of neutral salts are added to the blood.

[1] Paul Bert. Lessons on the Comparative Physiology of Respiration, page 88. Paris, 1870.

CHAPTER XIX

Transfusion of Blood—[*Continued.*]

Different methods of transfusion.—Apparatus.—Expected effects of injected blood.—On the selection of blood, whether arterial or venous, animal or human.

GENTLEMEN :

In our last lesson I mentioned the use of neutral salts for the purpose of preventing the coagulation of blood. Phosphate of soda, and carbonate and nitrate of potash, are the salts generally used ; they are taken from the blood serum itself, and really prevent coagulation. But nitrate and carbonate of potash are objectionable, because they have a poisonous effect, and Pavie has proven that, in a great number of circumstances, blood kept fluid by means of these salts has acted toxically upon animals. They have, therefore, been abandoned.

Sulphate of soda is chiefly used. Prevost and Dumas have employed it in doses of 14 per 100, and even per 1000, and it has proven itself an efficient obstacle to coagulation. But in small doses it hastened coagulation, hence it had to be used in large quantities, and has therefore been given up.

It was then suggested that the blood should be defibrinated.

At first thought this method strikes one as irrational, because blood being an aggregate, the globules cannot be isolated from the fibrine and the plasmine without suffering great damage, and, consequently, endangering the success of the contempla'ed operation. Hence, this process has, from the first, been denounced by able men.

Magendi pronounced against it by saying that natural blood, retaining all its principles, was alone capable of sustaining life. Poiseuille also said that without its fibrine, blood could not be

of any service. Desgranges and Devay maintained that globules, when beaten, are as good as killed; Giraud-Teulon also preferred the whole blood. Roussel, of Geneva, who, of late years, has even made a scientific tour for the purpose of establishing the great importance and efficacy of his method for the transfusion of blood in the veins, has likewise declared that the failure of a certain number of operations, apparently under favorable circumstances, was due to the fact that defibrinated, that is, a bad quality of blood, had been used; finally, my regretted colleague, Béhier, in his picturesque language, exclaimed that blood beaten to death was blood which, henceforward, should never be used. Still the contrary opinion for a long time prevailed, and does yet in the minds of a number of practitioners, among whom we find many illustrious names.

Messrs. Prevost and Dumas were the first to use defibrinated blood. They observed that this blood contained, apparently, unbroken globules, which retained not only their form, but also their chief properties. These observations have, of late, been confirmed by my friend, Prof. Brown-Séquard, who has made on this subject, experiments that appear conclusive. He saw that the globules of defibrinated blood had lost their aspect, their conformation, and their dimension; but they reddened when in contact with oxygen, and grew black under the influence of carbonic acid. He observed that when introduced into the veins of bloodless subjects, who were at the point of death, they produced the same physiological effects he had demonstrated belonged to arterial blood, that is, a very evident excitation, not only of the nervous centres, but also of the contractile fibres, either of relative or organic life. For example, they excite the movement of the intestine and awaken the respiratory functions, which circumstance illustrates the physiological action of the substance used. Hence, these experiments seemed to justify the idea of defibrinating blood. I must add that a long series of cases could be appealed to, in which the injection of defibrinated blood had, apparently, given good results. If, on the one hand, we consider the physiological experiments, and, on the other, the therapeutical

results, it is difficult not to admit that this process is good in itself, and that it probably answers all practical purposes

Yet, such is not the case; in experiments and observations all coincidences should be laid aside. There are many cases in which an animal, even when exsanguine and at the point of death, returns, unaided, to life.

According to Mr. Vulpian, this circumstance renders all conclusions very difficult, because, even when three-fourths of an animal's blood has been withdrawn, it may yet survive. But here a great number of positive facts may be called up, which form a series of lamentable failures. That is, where, in the midst of favorable conditions, and when the injection into the veins should have restored life, it has been seen to pass away without recourse. These unfavorable cases are in greater number than when blood, in its natural state, is used.

Another point to be noticed is, that not only is the method useless, but it is even harmful. It has been observed, in a number of cases, both among animals and men, that the introduction of this defibrinated blood, has given rise to serious, grave, and really poisonous phenomena, consisting in nervous movements, convulsions, and, finally, in death. These phenomena were, evidently, in proportion to the quantity of blood introduced; with men, they showed themselves in less marked form; but they were fully displayed among animals, with whom a more liberal quantity of blood had been used.

Moreover, it might have been thought that by defibrinating the blood, by only leaving the serum and the globules, we would, at least, have been secure against accidents from emboli; this is not the case, however, and Mr. Vulpian told me that in a number of experiments made by him, he had, on the contrary, found that thrombi had often been the cause of the animal's death, in whom these injections had been made. The reason of this is, that although care has been taken to strain the defibrinated blood, so as to avoid the clots, it is impossible to guard against those which, although invisible to the naked eye, are yet of considerable importance when we consider the calibre of the least order of

capillaries. These little grumes are enough to produce capillary emboli, and, consequently, accidents of comparative gravity, if these infarcts are numerous. I must add that even in cases where results were favorable, they were not lasting.

The re-animation of the organism in which the injection had been made, was shorter than with blood in its natural condition. These results could have been foreseen, and so they were, by physiologists.

For my part, I was convinced such would be the case, because the globules are not only suspended in the serum, but each one is surrounded by an atmosphere of plasmine; if the number of globules in the blood is reduced, the proportion of plasmine becomes excessive; it is then free, and capable of being eliminated through the emunctories, which serve as passages for the proteinous matters. For this reason, when the number of globules in a patient becomes reduced, albumen shows itself in the urine. In a word, the globules seem to be a centre of attraction, around which certain portions of albumen congregate. The removal of this plasmine endangers the nutrition and life of the sanguineous globules. Everything, at present, concurs in proving this to be the correct view.

When blood in its natural state is used, we are met by all the objections urged against coagulation. But now, thanks to an improved apparatus, blood drawn from a vein is so rapidly injected, that it has neither time to coagulate nor to mix with air. It is true that only venous blood can be thus introduced, but we shall presently see that this is no unfavorable condition, and that, in fact, it is a matter of indifference whether venous or arterial blood is used.

In the instrument invented by M. Collin, the blood is received in a cupule, which has first been heated by means of hot water to a temperature of about 38° (blood is at + 37.5°); this temperature remains about constant while the operation lasts; the cupule is connected with a pump-barrel for the purpose of injecting the blood. The improvement in the instrument consists in this, that the cupule and pump-barrel are con-

nected by a tube in which there is a little aluminum ball, whose specific gravity is less than that of water, and, of course, much inferior to that of blood. When blood is poured in the cupule the ball rises, and communication is established with the pump; as blood is withdrawn, the ball descends and prevents the air from penetrating along with the blood in the pump-barrel.

This apparatus is of great simplicity and easily handled. By its aid, not only is the necessary quantity of blood readily drawn from the vein of the one supplying it, and we shall see that for the purpose of awakening life in a person at the point of death, this quantity need not be large, but the blood is rapidly injected without carrying with it any of the gases that might favor coagulation, and what is of vast importance, without any air being introduced into the veins.

Let us now examine this question from a scientific and practical point of view, and understand the part acted by the blood in its natural state when injected into the economy.

It has been said by some that it acts only as a stimulant, others claim that it is a real life-regenerator; probably, as is generally the case, the truth lies between the two extremes.

But, in the first place, I would have you remark that blood in its natural condition, such as we at present introduce, has three parts to perform.

In the first place it brings nutriment. In the case of an exsanguineous individual, who not only has lost globules, but also all protein matters intended to maintain the nutritive integrity of all the organs, injected blood supplies him with plasmine and the elements of chyle.

In the second place, blood also brings oxygen, which favors combustion, but this is not always the case, because it is mostly venous blood which is introduced.

In the third place, it especially carries globules, which are the principal agents of hematosis and the nutritive phenomena. The blood globules are a vehicle for the gases, they bring oxygen into the organs, and carry away carbonic acid, and by means

of this exchange calorification, and therefore nutrition, are maintained in action.

Besides, as I previously stated, the globules are necessary centres of attraction in order that the blood may preserve its normal constitution; from the moment they so decrease in number that a large proportion of the plasmine is set free, serious suffusions are everywhere formed and create a new source of danger to life.

You may urge that defibrinated blood supplies all these wants; but I will now show you that it does not.

Defibrinated blood supplies dead or dying globules, which still retain the property of absorbing oxygen and carbonic acid; they are able, for a short time, to perform the functions of globules, provided their structure is not impaired. As I stated, when globules are deprived of plasmin, their vitality is impaired, and this explains how, in a number of cases, results have been so instantaneous, and why, in others, toxical phenomena have followed. These latter are very easily understood since the experimenis made by Paul Bert, because we know that when a large quantity of impaired globules, or natural hemoglobine, is introduced into the circulation of an animal, not only does it derive no benefit from the treatment, but it may become poisoned, and even be killed. There are also cases in which a large dose of such blood in the human system has produced real toxical accidents; even paralysis and death. At all events, as I remarked, it is only for a very brief moment that these perishing globules are able to continue the functions incident to their structure, for, as I have had frequent occasion to point out to you, the organic properties belonging to structure are independent of life; life may become extinct in an organ, and that organ may still conduct a nervous current, or else contract itself under the influence of excitants. In the natural blood, which has lost none of its indispensable constituent elements, and which has retained not only its serum, but also its plasmine, the globules preserve their vitality, and consequently their effects are far more lasting than those of globules taken from defibrinated blood. The continuance of

these effects, however, is not unlimited, because, while we do not know the duration of globular life, we have reason to believe that it does not extend beyond a few days—nay, perhaps not over a few hours. But a few days of functional activity communicated by the introduction of new blood, may be the means of saving life in a great number of cases.

Now, the question is, have the globules in new blood the power to determine the formation of native globules in the blood into which they have been injected? In other words, when new globules are introduced in an exsanguine animal or in a woman who has experienced profuse hemorrhages during labor, have they the faculty of developing, *proprio motu*, other globules, or of favoring their development? By some this is unhesitatingly answered in the affirmative; for my part, I believe new blood can indirectly favor the generation of red globules in the organism into which it has been infused, but it is doubtful whether this is directly possible; in fact, it may even be looked upon as impossible, because globules are not reproduced by fissiparity. Hence they can only act indirectly as a stimulus to the organism, and consequently to formation and nutrition.

Nutrition, and the recruiting of organs already formed, is a similar phenomenon to that of fecundation, according to the revelations of Aristotle and of my teacher, Lallemand. Therefore I say that by means of this stimulating influence, exerted over a failing organism, it is possible that these globules favor that formation. They may even contribute towards it in another way, because we know that organs are formed under the influence of particular conditions; hence, from the moment that these conditions are present, the genesis of these organs will take place in a more active way.

We know that the blood globules are not formed in the blood. I am inclined to think they originate in the lymphatic system, but in order that they may acquire their development the presence of a certain number of blood globules is necessary. I have long ago advanced the opinion—and the subsequent development of certain theories in Germany lead me to believe I was in the right

—that a communication exists between the lymphatics and the veins, and that the object or effect of this communication is the introduction into the lymphatic system of blood globules, which act the part of allurements or suggestions for the formation of new globules. In this way we can understand that when globules are injected, they may be able to favor the genesis of other globules. We should also take into consideration the influence exerted by the power of numbers.

Now that we know what may be expected from blood in its natural and intact state, when injected into the veins of subjects requiring globules, let us ascertain whether arterial or venous blood should be selected. On this subject the greatest differences of opinion exist among writers.

There are those who insist upon arterial or arterialized blood. Others, on the contrary, are content with venous blood, and a few, even, give it the preference. In order to discover which opinion is correct, let us first examine the real differences existing between the two bloods. My friend, Brown-Séquard, has long ago fully settled this point. He has shown that arterial blood is best for the purpose of increasing the vital energy of the organism. Let me borrow from the old medical nomenclature a very correct and expressive phrase: *Arterial blood increases radical force.* Not acting on the nervous system, it does not awaken that complication of symptoms which I have described. It is a way of increasing the vital energy.

According to the same author, venous blood is, *par excellence*, a stimulant. It gives rise to all the functional manifestations I have mentioned, but, on the other hand, it does not increase strength, nor the real vital power. It therefore calls into activity the functions, when these are more or less languid.

In other words, while arterial blood increases the radical forces, venous blood seems to augment the acting forces. This is also a distinction I have endeavored to establish between continuous and interrupted electric currents. A continuous electric current is a means by which the organs can be charged. An inductive cur-

rent is a way by which to excite them. I have already given you illustrations of this theory.

It seems difficult to establish a choice between arterial and venous blood, equally urgent reasons recommending them to experimenters. Brown-Sèquard decides in favor of venous blood, because it is a stimulant. He believes it should be introduced, as it has the power of awakening the functions of the respiratory and circulatory apparatus, and that it is through those that animals and also human beings perish when they have suffered very heavy losses of blood. However, Bischoff, in his experiments, has noticed that venous blood kills an animal more rapidly than arterial blood taken from another animal. That is, for example, if the venous blood of a sheep is introduced into a goose, it will die quicker than if arterial blood had been used. This proves nothing, except that birds have a mean temperature equal to the maximum or pathological temperature of other animals, consequently combustion in them is very active, and therefore they perish sooner when deoxidized blood is injected into them, than when blood is introduced which is still capable of momentarily galvanizing their organism. Hence, Bischoff's experiment is of but little value against the use of venous blood. Nevertheless, a great many writers give the preference to arterial blood, basing themselves upon the knowledge we have of the usefulness of oxygen in respiration, and consequently in the whole functional action. They contend that under all circumstances it is best to introduce into the organism blood laden with oxygen, because during the course of circulation this gas will determine all the effects of combustion, and consequently will more readily awaken an organism undergoing destruction. Evidently this view is a very correct one. But let me remark, that when we make a transfusion upon a man, we do not intend to galvanize his system, but we desire to bring to him powers that have persistence, that will live a given length of time, and that are able to keep up the functions in the patient as long as necessary, and until he is once more able to form globules.

Under these conditions it is of little importance whether at the start the blood used is charged with oxygen or carbonic acid.

In the first place, arterial blood cannot be procured without much trouble, for an arteriotomy can only be performed on an animal and not on a man. However, to this there is one exception. I have seen my teacher, Trousseau, perform arteriotomy on the temporal artery, that is, on an artery resting on a resistant plane, over which compression is easily effected. He performed this operation without any danger in cases of facial neuralgias resisting all other methods. (The operation would be censured at the present day, but at that time aconitine was unknown.) If arterial blood is required, it is from there it should be procured. Venous blood could be arterialized by being compressed with oxygen, or agitated with air. But this is a bad process. As I have told you, agitation favors coagulation, even if the mingling of gas with the blood had not the disadvantage of introducing air into the veins.

Dr. Gesellius has invented a process for obtaining arterial blood, which he believes practical, but which is not. It consists in pumping the blood from the capillaries of some fleshy portion of the body. But the capillaries are not all arterial, and the blood thus obtained is in great part venous. This does not even answer its intended object; besides, it is difficult to obtain thus the necessary quantity of blood in a sufficiently fluid state, not to cause emboli.

Hence, as you see, on the one hand, the having arterial rather than venous blood is not of great importance; and on the other, it could not be obtained without danger to the one supplying it. Consequently, venous blood has come into general use, and, while it does not supply strength, it at any rate produces stimulating phenomena, which probably, at the first moment, are of greater utility than strength itself. In fact, in a great many circumstances, after serious traumatisms, the first requisite is to awaken the organic functions, stimulate the contractility of the cardiac muscle, and revive the functions of the circulatory system. For those purposes, therefore, it would seem that venous blood is preferable to arterial.

Humboldt favored the use of blood laden with chyle, because an exsanguine individual is incapable of digesting, and by that means he would be supplied with blood and aliments which he otherwise could not procure. If the use of animal blood was a matter of indifference, I might be in favor of feeding an animal and taking its blood while laden with chyle; but we cannot ask a man to imperil his life by giving his blood during the process of digestion, when we know that blood-letting, under those circumstances, is highly dangerous. Therefore, this is a method which cannot be applied, and it is of but limited utility as an adjuvant when an object is simply the introduction of globules.

We are here met by a very serious question, which is, whether the blood of animals can be employed, or should we limit ourselves to the use of human blood? In the early stages of the method the blood of animals has been used, and Denys reports a number of examples which indicate that this has been done with safety. But I will show you that it is not absolutely devoid of danger, and that it is best only to use human blood.

CHAPTER XX.

Transfusion of Blood—[Continued.]

Quantity of blood to be introduced.—Manner of operating.—Who should supply the blood.—Venous transfusion.—Mediate and immediate effects of transfusion.—Indications and counter-indications.

GENTLEMEN:

At first thought it would seem that in order to restore the regular functions of a depleted organism, it would be necessary to return to it the full measure of blood lost. This, however, is not the case. Small quantities are sufficient to produce re-animation; larger doses would be superfluous, and very large doses would really prove toxical.

When very large quantities of blood are introduced into animals, they produce accidents of a nervous nature, troubles in the motor and sensory systems, and real convulsions, which may result in "sideration," according to the sense now given to this word, and finally end in death from a sort of rapid syncope.

These phenomena may be explained in two ways. In the first place, by a sort of traumatism, for Waller has proven that when a quantity of new blood is introduced, the vascular system, which was already distended, suddenly develops such an amount of resistance that serious accidents immediately follow, caused simply by mechanical effects. It is said that under such a shock the heart ceases beating. But besides this vascular repletion and all the accompanying phenomena, there is also a state of real intoxication, which results from an accumulation of the products of globular denutrition in the blood of the individual receiving the new blood. The effects of this blood are not those of real poisons, but, as you know, whenever the economy is burdened

by any kind of refuse from denutrition, the organic functions become seriously impaired. These are what I have called cases of passive poisoning. For example, when there are large quantities of urea in the blood, if it becomes an obstacle to organic renovation, after a time the old and worn-out organs are no longer able to fulfill the requirements of the organism and the patient dies. The same phenomenon takes place upon the introduction of a large quantity of new blood. Its globules not being long-lived, finally become an encumbrance to circulation, and in consequence are a cause of reduced activity for all the functions, in place of being the cause of stimulating and even vitalizing effects.

Very copious injections can, however, be made. Mr. Richet succeeded in introducing 1000 grammes of blood into the body of a human subject, but this was done with extreme slowness, so that each dose introduced could not produce either the mechanical or the general serious effects of which I just now spoke, and which are the result of a species of intoxication.

But we need not occupy ourselves with the effects attending the injection of a large volume of blood, since a small quantity is sufficient to produce a satisfactory result; and the re-animative power of a small proportion of blood seems to be so great, that a very moderate quantity appears quite sufficient. As an illustration, here are some figures: Desgranges and Devay have injected 180 grammes; this is a great deal—it is a maximum dose. In other instances, 90, 80, 75 and 60 grammes have been injected. In two cases recorded as successful, 7 or 8 grammes of defibrinated blood were used. These are all very moderate doses. In other cases, we are told of 120 and 730 grammes; and, finally, Mr. Richet injected 1000.

Taking into consideration the last transfusions which have been made, we shall find that a dose of 100 grammes has not been exceeded, and yet good results have been obtained. The same may be said of the cases reported by Briquet, Dolbeau, Maisonneuve, Lorain, Brouardel, Maurice Raynaud, Féréol and Straus, which have all been successful. As you see, the doses

are not large; the maximum injected has been the 5th, at times the 50th, and, most frequently, the 500th part of the total mass of the blood. Consequently, transfusion may be successfully accomplished without having at one's disposal, a very considerable source of blood.

With regard to selecting the person who is to supply the blood, we should, as far as is possible, choose a young, healthy and vigorous man; and, in general, at the present day, there is no trouble in finding those who are ready to contribute their blood for the relief of others.

Let us now consider the choice of a vessel, and the necessary preparation for the operation. Here, again, we are met by a double series of processes. As a rule, an intravenous injection is made, and as the blood is taken from a vein, it is "venoso-venous." Of late years, it has been thought best to do away with the use of an instrument, and to inject the blood directly into the circulatory system of the one who is to receive it. This, however, would require that the blood should be taken from an artery whose propulsive force could cause the blood to penetrate into the patient.

Mr. Roussel has traveled over Europe for the purpose of establishing the efficacy of this method. In this process the arterial blood is to be procured either from an animal or from a man. But how can any one assume the responsibility of opening a man's artery for the purpose of transfusing blood? Therefore the arterial blood of an animal has to be resorted to. Here, however, there is a difficulty, for I have shown you that this blood does not give the same results as blood from an individual of the same species. Besides, why incur all these dangers, when the results are not any more successful?

Among 28 cases of venoso-venous transfusions, there have been 10 deaths, 2 remained stationary, and 16 were followed by improvement or cure. In other instances in which the arterial blood of animals has been transfused, the results have not been so satisfactory. This method is not any more successful than

another, but is surrounded with dangers; therefore it is not entitled to the preference.

In venoso-venous transfusion, the use of an instrument is necessary, because direct introduction is very difficult. The basilic vein is generally chosen; an incision parallel to the vein is made, and a ligature is placed above it. A V-shaped incision is made in the vein, and the canula, through which the injection is to be made, is introduced into the vein; an intelligent assistant holds the vein upon the canula, and the operation is very simple.

Plain and complicated instruments of all kinds have been used, but, of late, very simple apparatus has been chosen; in fact, much too simple, for, in a number of cases, an ordinary irrigator has been employed. Desgranges and Devay, and others, have used a hydrocele syringe, more or less modified; these are very simple instruments, but, like all those in which agitation takes place, they afford no security against coagulation and the introduction of air into the vein. At present, in the way of easy and efficient apparatus, we have that made by Mathieu, and the one invented by Colin, which I described in the last lesson. Both are so practical that we need no longer hesitate at practicing transfusion whenever the operation appears necessary.

Having chosen the one who is to supply the blood, and the region, the vein is prepared and the blood-letting takes place; next follows the operation. The blood is received as near as possible to its exit, so that the venous fluid has neither time to break its globules nor to coagulate before it enters into the funnel of the instrument.

If the object is simply a stimulating effect, a momentary revival of the patient, then globules in defibrinated serum will answer the purpose. But if you look for lasting results, for a re-animating injection, which is to place the subject under favorable conditions for a return to life, in that case the blood must be natural, intact, and in possession of all its elements. Under those circumstances the liquid blood is received in the funnel of the instrument, and a given quantity, say from 100 to 150

grammes is made to penetrate with due moderation. That quantity should not be exceeded; but we must proceed without haste. When this is accomplished, the instrument is withdrawn, and a dressing is applied the same as after blood-letting.

Objections of all kinds have, however, been urged against transfusion. Although, as I have shown you, the operation is a simple one, and when properly practiced is generally exempt from nearly all disadvantages, still faults, drawbacks, and even dangers have been laid to its account.

It has been declared that no good results could be expected from transfusion, because the globules we each possess are peculiar to and can only serve the one individual. This was a prejudice; experiments made on a large scale prove that, in reality, transfusion produces very good results, which are not only immediate, but also lasting, and that it has been the means of saving a great many lives.

It has been said there is danger in substituting the blood of one species for that of another. This is no doubt true in certain cases, but the blood of fishes has never been introduced into the veins of man; use has been made of the blood of calves and other animals having small circular globules, which can cause no ill effects.

The dangers of virulent inoculation have also been mentioned. But these exist everywhere, even in vaccination. Instances are on record when vaccine matter has been a vehicle for syphilitic infection. All we can do is to be careful in the selection of a subject, and he who offers to contribute his blood must feel sure of its purity.

The formation of emboli by clots or fibrine, and the introduction of air, have been spoken of as dangers inherent to the operation. These certainly existed when the apparatus was imperfect. But improved instruments have done away with all risks, and, of late years, among a number of operations which have been performed, we have never heard any mention of emboli or infarcts. It has happened that transfusion has not always

succeeded in saving life. This has not been through any fault of the operation, but owing to the condition of the patient.

Phlebitis and purulent infection have also been spoken of. These are possible; but phlebitis shows itself chiefly when a ligature has been applied too tightly; if, on the contrary, the vein is held by fingers that know better how to measure pressure, there will be none of those rude attritions of the inner membrane of the vein, which eventually develop phlebitis, or give rise to the formation of a thombus.

As regards pyemia and purulent infection, one might as well say we should, on their account, never practice blood-letting. We can, besides, always place ourselves on the safe side by removing the subject upon whom the transfusion is to be practiced, into pure air, and placing him under such conditions of ventilation that purulent infection need no longer be feared. In conclusion, the operation is at present easy, exempt, we may say, from any objections; and I shall now tell you what results may be expected from it.

When a considerable quantity of more or less generous blood is first injected into a subject who is excessively pale and laboring under the effects of deep anæmia arising from hemorrhage, the face is seen to revive, the eye brightens, and the pulse, if very weak, picks up and acquires some volume; if it was quick, it becomes more moderate, even calorification is somewhat reproduced, and warmth extends to the extremities. These are the first effects; there are others which are consecutive.

There is an awakening of all the leading functions, as of respiration and nutrition, and this awakening bears no proportion to the quantity of nutrient materials, of globules, which is introduced. In a majority of cases it would seem this spurring is enough to arouse an organism apparently very seriously impaired. We shall notice a marked improvement in the muscular forces, the voice returns, the nervous functions resume action, the patient recovers sensation, the intellect, which was obscured, revives, so do the special senses—there is a general revival, which is gradual, or at times somewhat speedy. Appetite

returns, so do the digestive faculties and sleep, which had been replaced by narcosis. If the patient has been subject to nervous phenomena, such as slight muscular spasms or convulsions—for you know that when the blood is greatly diminished, convulsions take place resembling those in epilepsy or a rush of blood to the nervous centres—those phenomena cease. It would not avail as much if we only had these results, and if there did not remain a deep and durable re-animation enabling the organism to recruit itself. This also takes place providing the cause inducing anæmia is not a persisting one, and on condition that you are not in the presence of a necessarily fatal illness. If you are dealing with one of those organisms which, for some reason, cannot be re-animated, but which you galvanize, (this is the best expression), by means of transfusion, you will find that after a time, either a day or forty-eight hours, the organism again sinks, all the functions become languid and lapse into their previous condition, and you find that the increased proportion of globules, of which you had determined the number, has also decreased.

I witnessed a case in which the operation was performed by Dr. Brouardel, at Beaüjon. Before the operation there were 3,200,000 red globules; 150 grammes of blood were injected and the number increased to 3,500,000. At the end of thirty hours the number of globules fell back to the first figures; the patient died, and this showed us that with his own powers he was unable to make globules. This suggests to you a way of ascertaining the exact condition of your patient.

The question has been asked whether repeated transfusions cannot keep up a sort of artificial life, and thus finally permit a return to health. It would seem not; on animals the experiment has given no good results, and it has hardly been tried on man.

A number of dogs have been taken and deprived of solid food, but they were given all the water they required. To a portion of them repeated transfusions of blood were made. The first lived twenty-three days, the latter died at the end of twenty-eight, although they were continually supplied with considerable

quantities of blood. This shows that a supply of blood and globules is not alone sufficient to keep up life, but that the digestive organs must be called into action, they must receive food, and this food must be assimilated and perform all the functions required of it by the economy.

I shall now speak of indications and counter-indications, and I ask leave to divide transfusion into several categories. We first have *preventive transfusion*, intended to prevent accidents arising from extreme anæmia; then *repressive transfusion*, whose purpose is to remedy the various evils caused by this anæmia. This last should be divided into *palliative transfusion*, that is, by the use of defibrinated blood, and really *curative transfusion*, which is practiced with the blood in its natural state.

Preventive transfusion. For example, an individual meets with some terrible accident; he is picked up weltering in his own blood, he revives, and his recovery depends upon an operation entailing a further loss of blood. Evidently a surgeon would hesitate at such an operation unless he had the means of recruiting that organism so entirely depleted of blood. If, by the aid of a transfusion made prior to the operation, he is able to supply the patient with perhaps a greater quantity of blood than he is likely yet to lose, the operation will thus become possible and very useful.

Let us now consider *repressive transfusions*.

We first have *palliative transfusion*, intended for a momentary revival of the organism. This can always be practiced, for there is always advantage in recruiting a patient's strength, and Brown-Séquard has gone so far as to say that these transfusions are advisable even at death's door. If he only intended thereby to postpone the fatal issue for a few hours, the operation is hardly desirable, but perhaps he thought of possible errors in diagnosis.

Anyhow, without going so far, I will say that palliative transfusion, in a great many circumstances, may be useful and may be recommended.

Curative transfusion. This presents positive indications and counter-indications. Nothing can be expected from transfusion

when anæmia is caused by a cancerous cachexy or if it is due to leucæmia, or to hemorraphylia. (You will notice, I do not say *hemophilia*, and that I use the *y*.) These diseases cannot be fought in this way.

If you have to contend against poisonings caused by a deep organic lesion, or by a number of organic lesions, as is the case in uræmia, in which the kidneys have suffered degeneration, no benefit will attend transfusions of blood exempt from urea, no matter how often these transfusions are repeated. You will meet with no better success in septic diseases, because the poison is being continually renewed. As to old age, that is an ill from which there has been no recovery, since the waters of the fountain of youth were dried up. It is said an old dog was made young by transfusion. I am afraid, however, this was drawn from the imagination. I say the same of a number of pathological conditions which have been considered amenable to this operation. Denys reports having injected the blood of a calf into a raving maniac, and that he had been improved. It has since been suggested that the disposition of persons could be modified, especially of those under pathological conditions, if the blood of young and mild-tempered persons was introduced in their veins. This, of course, does not deserve attention. But real curative transfusion can, on an emergency, be of service in troublesome conditions, such as essentially spontaneous anæmias. In chlorosis, when very strongly-marked anæmic phenomena are associated with that serious condition, there is no reason why transfusion should not be practiced. There are chlorotics who are in such a state of globular depletion that they can hardly walk a single step without being quite out of breath. It is evident that if at this period of their ailment generous blood is injected into them, they will be greatly improved. Purpura and scurvy would also warrant injections. Albuminous and saccharine diatheses, accompanied by very marked anæmia, may be counteracted by this method.

Constrictions of the œsophagus and certain more or less serious affections of the stomach, which form a considerable obstacle to

alimentation and consequently also to nutrition, admit even more of the introduction of blood taken from a healthy and vigorous subject than of the introduction of peptones into the cellular tissue. But there are positive indications for it in certain cases of serious syncope, with subjects who have lost a moderate quantity of blood, but who are enervated by a moral shock, and present the semblance of apparent death, cases allied to those which Dupuytren called *nervous blood-lettings*. In those cases, as in those of lethargy, blood might be injected with advantage. Also in certain asphyxias and intoxications, in which death is imminent; when, for example, the globules have become impregnated with oxide of carbon, if it is possible to withdraw a portion of that blood and replace it by another which is pure, and capable of keeping up respiration and the other important functions, you will in this way save your patient.

It is not probable that for some time to come, the foregoing advice I have given will be acted upon. An ordinary case for transfusion is inanition, where subjects have been deprived of food for a long time. Such an occasion would be an excellent one for injecting blood. Further, in certain exhaustions, such as those which follow prolonged suckling or losses of blood of all kinds, you may still momentarily revive the subject and prevent a continuance of the exhaustion. It is the same in cases of incoercible vomiting; and especially in very abundant hemorrhages following an accident, or else that physiological traumatism which follows the puerperal state. It is above all among women after labor, when nothing has been able to put a stop to these hemorrhages of one, two, and sometimes more kilogrammes, that transfusion becomes absolutely necessary, and that dependence must no longer be placed on the natural efforts. Among ninety-three transfusions practiced in cases of this kind, no less than sixty have resulted in the cure of women who were so thoroughly exhausted that they were in a dying state. This is undoubtedly a good result.

Unfortunately there are but few indications by which we can judge when there is a necessity for transfusion. Profound col-

lapse, torpor, and weak pulse have been mentioned as signs, but these are very vague. With animals the case is different. We can take precautions, and, guided by the use of the scales, it is easy to establish the following rule: when an animal has lost by hemorrhage, according to some, an eighteenth, according to Milne-Edwards, a twentieth of its weight, it is then time to interfere. But if you reflect what the eighteenth part of an animal's original weight represents, with regard to the total quantity of blood, you will find that, admitting 5 kilogrammes as the average weight of blood in a man weighing 60 kilogrammes, he will have lost three-fifths of the total mass of his blood, or else four-fifths, if we admit the basis of a twentieth. Four-fifths of the blood is enormous. There would then only remain a single kilogramme of blood in the economy. This is about the same estimate that can be reached by other considerations which I shall indicate. But, unfortunately, we can have no knowledge of a woman's weight prior to her losses, hence we can form no estimate of the quantity of blood lost, especially as it is scattered all around and through the linen which it soaks.

There is a process by which the retrospective diagnosis of the situation may be established. This is as follows: In the operation performed by Dr. Brouardel, (I select that case because the globules were counted,) he injected 150 grammes of blood, representing 19 grammes of globules. If we rely upon the known composition of blood, this blood was enough to make an increase of an eleventh in the former proportion of globules, since 3,200,000 were raised to 3,500,000. There were, therefore, 190 grammes of globules in all, since 19 grammes represented an eleventh. Now if blood is in the ratio of 127 or 130 grammes of globules to the 1000, we find that there must only have been 1.500 kilogrammes of blood in the patient.

But allowance should be made for the fact that the globules must have been diluted in a large quantity of serum, in the ratio indicated between 3,200,000 and the average figure of 5,000,000. Therefore there was about five-twelfths of water in the patient's blood, that is to say, that to the 1.500 kilogrammes which we

find by calculation, we have to add five-twelfths—that is, 625 grammes—which gives us a total of 2.125 kilogrammes. Therefore this patient, whose condition was so serious that transfusion was deemed necessary, had but two-fifths of the normal quantity of blood left in him.

Thus, by the aid of a calculation, I have reached the same numerical result as experimenters have, who make their observations on animals. From this it follows that there is indication for practicing transfusion whenever the patient has lost three-fifths of the total amount of his blood. Only, as I remarked, it is a pity that you cannot tell, before practicing transfusion, what is the quantity of blood remaining in circulation.

I am now through with the history of transfusion. It may have appeared tedious to you, but the subject is a very interesting one and daily growing in importance. Much attention is being bestowed upon it, and if we take the total number of transfusions which have been made, including even those with defibrinated blood, however incapable they were of realizing the hopes placed upon them, since they could but temporarily revive the organism, we shall find that out of 270 cases of transfusion there have been at least 150 successes.

I therefore sum up with the conclusion that when a method is easily applied, is exempt from real dangers and gives such results, when death is almost imminent, it should be recommended, and full credit is to be given to those who are endeavoring to extend its use.

CHAPTER XXI.

Injections into the Blood.—Transformations Undergone by Medicaments.

Medicinal infusions into the blood.—Intravenous injections.

TRANSFORMATIONS UNDERGONE BY MEDICAMENTS IN THE ORGANISM:

Immediate Changes—Nitrate of silver.

Changes in the Primæ Viæ—Temperature.—Cold drinks.—Negative functions of the mouth.—Active functions of the stomach.

Modifications in the Intestine—Functions of fatty bodies, and of albuminous matters.—Gas.

GENTLEMEN:

Let me now briefly notice *medicinal infusion*—that is, the introduction of medicinal substances into the veins. This operation is not as ancient as the transfusion of blood, although it is more simple and apparently more natural. As I stated, both it and transfusion were proffered to the Bishop of Exeter. It would seem Fabricius likewise practiced the infusion of medicines into the veins. But it is really only in the early part of this century, about 1802 or 1803, that Doctor Scheel revived the practice. Since then it has been often repeated, but never under favorable conditions. The fact is, as I shall hereafter point out to you, there seems to be no occasion for this operation, which we can very readily replace by other methods.

Tepid water has been injected into tetanic patients. The great physiologist, Magendie, succeeded by this means in stopping the spasms, but this did not prevent the patient from dying at the end of two days. Bennett repeated the same experiment and met with like results—an immediate discontinuance of tonic convulsions, followed by a fatal termination within a given time.

It was especially during the prevalence of cholera epidemics that the use of these intravenous injections was in favor. In this disease, death seemed to be brought on by the subtraction of a large quantity of serosity from the blood, since nothing but pure serosity is poured into the intestine—so much so that the pulse becomes imperceptible. It was, therefore, thought that some benefit could be derived by injecting into the veins water containing the salts belonging to blood serum. As the belief prevailed that sulphate of soda, when injected into the veins, was a purgative of considerable energy its use was avoided, and in its place more or less diluted solutions of chloride of sodium and bicarbonate of soda were used. The immediate results appeared very favorable. I have even seen persons who seemed revived, in whom circulation started a-fresh, but notwithstanding this they died, because this method availed but against one of the toxical symptoms and not against the persistent cause which determined the fatal results.

Natural serum has been injected without giving any better results than the solution of carbonate of soda. Nor have a number of other medicaments when injected. Acetic acid has been suggested—no one knows why; but we could understand the use of laudanum, because it would contribute to the recruiting of strength. Solutions of strychnine have also been tried, because it seemed necessary to revive and galvanize the medullary nervous system. In company with Dr. Duchaussoy, I once made an intravenous injection of 20 centigrammes of sulphate of quinine and met with an absolute failure. Yet sulphate of quinine seemed well indicated as a means of action against a disease which has been compared to and behaves like a pernicious intermittent fever; besides, it could at the same time act as an antiseptic and an antizymotic, and thus answer a double object. But it had not the least effect in spite of all our anticipations.

Emetics and purgatives have also, at various times, been introduced into the veins, under the belief that their effects would be more prompt. As I before remarked, this was a mistake; the results could only be indifferent, since those substances must cir-

culate and be eliminated before they can act on the intestinal muscular membrane and on the mucous membrane itself.

Finally, a German physician injected castor oil into his own veins. A dose of 15 grammes has been mentioned. I have not read this figure in the text, so I cannot guarantee the dose, but I am inclined to believe it was 15 grains. However that may be, the operation appears authentic. The experimenter felt somewhat unwell, experienced a taste of castor oil in the mouth, had some intestinal troubles and a desire to throw up, but nothing in the way of an alvine evacuation. Therefore, with regard to a cathartic effect, the result was void.

As to neutral salts, laboratory experiments have proven that they are constipating and do not occasion diarrhœal stools; consequently, all such experiments, good for a time when science was undeveloped, should not be repeated now.

Although a great many active medicaments have been discovered, they have not been applied to intravenous infusions. Even morphine and strychnine, which are so generally used, have not been injected into human veins by this method; but with regard to experiments upon animals, we may say that almost every active substance has been tried. The reason of it is that while chemistry was placing at our disposal a number of active principles, there were other methods rendering their passage into the economy so easy that infusion was not thought of. It is only accidentally that physicians have been called upon to witness the effects of active substances when introduced into the veins, principally, when in a hypodermic injection the needle penetrated into a small vessel. This accident, as I have already mentioned, may be followed by the most serious effects.

Several cases of death from atropine took place in Paris, in 1867–68. In a number of these the quantity introduced under the skin was not large, and the patients had previously had similar doses, without accident. I have no doubt that in those cases the substance encountered some venous branch into which it was introduced suddenly.

Of late years a distinguished surgeon, Mr. Oré, of Bordeaux,

has made himself the champion of intravenous injections of chloral, which he proposes substituting for other anæsthetic substances, for the purpose of producing anæsthesia; he reported a number of apparently favorable cases, and several surgeons, principally foreigners, have followed his method. I consider it injurious. In several cases this plan has not caused any serious accidents; there have been no deaths; but death has taken place in a number of experiments. One might have though that the animals that perished were under different conditions from man, and that the same precautions had not been taken; but Mr. Oré himself has had one fatal case.[1] Several others have happened, due to injections in cases of tetanus; I do not pretend to say that the patients would not have died within a few days, but here they expired under the influence of an artificial poison. Those results are easily understood. When chloral is introduced into the veins the dose must be massive, and may be greater than can be tolerated by the organism under treatment; with chloroform we can always set aside the terrible agent we are applying, but here there is no way of withdrawing the active substance, the proper dose may be exceeded, and produce such deep narcosis that the revival of consciousness and the organic faculties may no longer be possible.

Another very serious disadvantage is the coagulation of blood in the veins. Chloral is a coagulent which can be used for tanning and preserving tissues. Mr. Personne lately showed us at the Academy a brain preserved in chloral for a very long time, and we know that chloral coagulates blood as powerfully as phenic acid does. Therefore, when you introduce a solution of chloral, it must be a massive dose, because if over-diluted it would produce a commotion of the heart. Thus you risk causing a coagulation of the blood, and giving rise to emboli, to infarcts, and to a suspension of life in some of the essential organs.

In conclusion, this method of intravenous injections has never

[1] Oré. "Chloral and Intravenous Medication." "Studies on Experimental Physiology; Application to Therapeutics, and to Toxicology." Paris. 1877.

been able to gain a foothold in French practice. It exists in other countries where they are bolder, but here it has been energetically rejected by the Academy of Medicine, and I fully endorse that course.

I have now to consider the *alterations undergone by medicaments.* This is a very long chapter in general therapeutics, and one that deserves careful perusal in all its details. I shall chiefly consider the modifications suffered by medicaments when they are applied upon surfaces, or introduced into the interstices of the cellular tissue, and shall follow these medicaments in their course through the circulation, and in the secretions, wherever they may be attracted prior to their final issue from the organism.

There is, however, a chapter in medicinal transformation which here deserves mention. It is that concerned with the changes brought about in medicaments by the preparations in which they are administered to patients.

Pills of nitrate of silver are prescribed under the belief that they produce a catalytic effect on the digestive membrane; that they act as a stringent, determine favorable modifications, and bring on a cure. But the fact is, nitrate of silver is never introduced, or if it is, then the quantity is so trifling that it is insignificant. When powdered nitrate of silver is mixed with bread crumbs, in a very few moments the silver is reduced, and chloride or albuminate of silver is formed. More than seven-eighths of the nitrate of silver is thus decomposed into metallic silver. After a few hours' standing, the preparation contains no more nitrate. This proves that theories should not be constructed upon facts that are not fully established, and that often a substance is supposed to be administered when it is not.

Let us now consider the mutations which medicaments undergo when in the organism. These changes are of a physicochemical nature. We shall study them in the *primæ viæ,* in contact with the surfaces upon which remedies are applied, in the blood, in the secreting organs, in the recesses of the tissues,

and finally in the natural reservoirs in which they remain for a given time after having been eliminated.

Among the physical changes produced in the *primæ viæ*, those of *temperature* are interesting, because they are very important.

When a cold drink is introduced, its temperature is elevated by subtracting heat from the organs with which it comes in contact; thus a local sedation is produced which gradually extends itself through the whole system, revealing itself in proportion to the reduction in temperature. In febrile conditions cold drinks are the most sedative agents, hence they have always formed an element in an antiphlogistic regimen.

Let us now examine the chemical changes undergone by active substances in the *primæ viæ*. As I remarked, these changes are of vast importance, and they exert a great influence on the ulterior results and the form and activity of the pathogenetic phenomena which medicaments determine.

You must bear in mind that throughout the organism there are everywhere substances possessed of comparative activity, and capable of modifying medicamental agents. Alkalies, acids and alkaline chlorides are everywhere to be met with. You will presently see that these different substances exert a very marked and often a decisive influence on the direction in which medicamental mutation takes place.

The mouth calls for no special remarks—food only passes through it on its way to the stomach.

The stomach contains substances which in their normal state are of very great activity, according to some physiologists; these are lactic, chlorhydric, or phosphoric acids. Normal ferments are likewise present, as pepsin and its two modifications, if you will concede them—that is, the coagulating and dissolving ferments. Besides these, there are accidental ferments borrowed from the atmosphere, or developed under the influence of changes produced in the organ itself, at the expense of the alimentary substances. And you will also find it to contain atmospheric gases, as well as water.

When organic substances are introduced into the stomach, they undergo all these influences, and if there is considerable gastric activity, as for example, during the digestive process, they will experience such important changes that it may happen their effects will be entirely neutralized. You introduce aconitine but obtain no results, not even with high doses. Atropine and morphine are subjected to the same destruction. Even quinine and the proximate alkaloids which are so persistent, are not able to resist being modified, so that at meal-time considerable quantities can be taken without obtaining the desired results.

You should always be on your guard against this species of stomachic digestion, which is a cause of reduced activity in medicamental substances. The only remedies which should be introduced at meal-time are those requiring previous dissolution, those acting in the same way as histogenics and metallic substances, from which the metal element is alone desired, such as iron, manganese and arsenic. For all the others another hour should be selected.

The acids in the stomach likewise exert great influence. They increase the solubility of salts, for, as you are aware, the majority of salts are rendered more soluble by an excess of acid. Bases are also salified by those acids. Thus the oxides of iron, of zinc and of calcium are salified and dissolved by the acids contained in the stomach. With regard to iron, this is of great importance, because we very frequently introduce oxides of iron, relying upon the acids in the stomach to effect their solution and procure their passage into the circulation. The acids in the stomach also decompose such carbonates as those of lime, soda, potash, magnesia and iron-rust. Consider how important are these facts. When you desire to diminish the gases and acids of the stomach, you must not prescribe carbonate of magnesia, but calcined magnesia. The carbonate would only have a tendency to increase the disorder by producing carbonic acid gas.

Finally, metals themselves, when free and introduced in an uncombined state, are dissolved by the acids in the stomach. However, this solution is due to a double reaction. These

metals are not directly soluble in the acids of the stomach, unless chlorhydric acid is present, and in sufficient quantities. They have first to be oxidized by the oxygen contained in the stomach. These oxides then combine either with the phosphoric or the lactic acids. Hydrogen is liberated and remains free, unless other elements are present ready to combine with it. When that is the case, if you administer iron to a chlorotic patient, she will have inodorous eructations—(pure hydrogen.) On the contrary, if the stomach contains albuminoid or nitrogenized alimentary substances in which sulphur enters, the eructations (formed of sulphuretted hydrogen, the latter having combined with the sulphur,) will be malodorous and have the smell of rotten eggs. You understand how important it is to fully comprehend those reactions, so as to know the disadvantages which follow the administration of certain medicaments, that you may explain them to the patients and avoid them.

In the stomach oxygen is also found. It has the effect of raising substances from a low to a higher degree of oxidation; that is what happens with sulphate or carbonate of protoxide of iron. It is important you should know that sulphate of iron can be of no possible service in globular recuperation. It might be continually and for years transfused into the veins of an anæmic patient without producing a single additional globule. Yet when sulphate of protoxide of iron is introduced into the stomach, the globules are increased. This is due to the process I have explained. It is converted into a sulphate of the peroxide of iron, which becomes basic. There is an ulterior oxidation, and a change to a higher condition.

This free oxygen oxidizes all substances introduced either at a low state of oxidation or absolutely free. Thus if sulphurous acid is introduced, it has been suggested that it will be changed into sulphuric acid. When phosphorus is introduced into the stomach, it passes to a higher degree of oxidation, and also undergoes other mutations due to the presence of water. Phosphorus decomposes water, and forms, on the one hand, phosphorous

acid, and on the other, phosphuretted hydrogen. Therefore, this is another kind of modification.

Let us now consider the mutations which medicaments undergo in the intestine. No doubt, we shall again meet with a number of those which take place in the upper portions of the digestive organs, but besides these there are others which manifest themselves.

If the stomachic liquid is acid, the intestinal is always alkaline, except that of the cæcum, which is said to be acid. However that may be, the alkalinity of the digestive duct is a general rule; it is due to the presence of bicarbonate of soda; when the acid substances from the stomach penetrate into the intestine, they encounter this alkali, which partly saturates them and liberates the carbonic acid with which it was combined. If substances acting the part of a base present themselves, combinations are formed, and by their aid these substances which of themselves would have been insoluble, are made to pass into the circulation, and produce their effects.

When colophony is introduced into the digestive duct, it is softened in the stomach, but in the intestine it can be dissolved, because there it becomes saponified, the same as all other terebinthines. They then form compounds which are called *resinates*, that is, in which the acid is represented by the resin. These substances then become soluble, pass into the circulation, and are carried, some towards the respiratory organs, others in the urinary organs, there to determine all the effects you know.

Substances which are only soluble in an excess of acid, are naturally precipitated when they enter the intestine and meet a liquid charged with alkali.

There is also a group of substances acting the part of solvents, and which, as such, have not been long known, but they are important, and deserve passing notice. I have reference to fatty bodies. They exist everywhere in the intestine, and are the solvents of such substances as sulphur, and especially phosphorus. Therefore oil and every other fatty substance should be carefully avoided in cases of poisoning by means of phosphorus.

Let us now consider the chlorides, which are everywhere distributed, but chiefly in the mucus. This you can verify by dropping nitrate of silver on mucus, when a white precipitate of chloride of silver will immediately be formed. The chlorides of the first groups have the singular faculty of combining with those of the last, so as to form real combinations in which the alkaline chloride acts the part of a base, and the other that of an acid. Chlorhydrates of chlorides are thus formed, having the property of being very soluble, while the others are very hard to dissolve. Thus, for example, take calomel, which is insoluble, and chloride of silver, which is but slightly so, associate them with a solution of chloride of sodium, and by the fact of this combination they will become soluble. Perhaps an exchange of base takes place. Mialhe believed that under these conditions the protochloride of mercury takes up part of the chlorhydric acid, and becomes a bichloride. But it may be, as has been believed, and as I think, that solubility results from the formation of a new salt. I have always opposed Mialhe's opinion, even in 1847, during Trousseau's time; I have made some mention of it in *The Art of Drawing up a Formula*, which is annexed to Trousseau's and Pidoux' treatise.

Calomel, for another reason, is not converted into bichloride, otherwise all we should have to do would be to give calomel in order to obtain mercurial salivation, which is readily produced by the bichloride. This clinical fact alone warrants the declaration that this is not the process by which calomel penetrates into the economy. We shall presently find direct demonstration in support of this.

We are thus brought to consider the importance of the albuminoid substances which are found in the intestine, and throughout the whole of the digestive duct. But their real mission is confined to the intestine, where they facilitate the penetration of different substances. They are not only emulsive agents, but perform the office of real solvents. It was formerly believed that those substances acted the part of gum arabic; that they divided insoluble substances, and by means of this division facil-

itated their introduction into the circulatory organs. That is not what takes place.

Albuminoid substances, such as albumen, the different kinds of mucus, and legumin, are real solvents for a great number of metallic substances, which they dissolve, because they combine with them. Real albuminates and leguminates are formed. Gluten might also be used, because it is an albuminoid substance. It is by means of the mucus that calomel is dissolved. This has been proven. Mr. Personne has made experiments in which he has dissolved calomel in mucilaginous substances.

It has long been known to chemists that albuminoid substances behave in a very peculiar manner when in contact with salts, such as those of zinc, copper, lead, silver, gold and platinum. When albumen is added to a solution of sulphate of copper a precipitate is formed; if more is added the precipitate re-dissolves, and it may be again reformed if still more is added. This same fact occurs with a number of other substances. I have had occasion to notice it with perchloride of iron, although this is a powerful coagulating agent.

These phenomena show themselves in a very marked degree, especially in the case of nitrate of silver, and they have been applied to good practical use in injections of that substance. When nitrate of silver is dissolved in albuminous water, this solution comes in contact with the intestine, without producing any strong chemical action, thereby avoiding the painful effects attending this action. The metallic salt gradually separates from its solution and acts upon the mucous membrane by modifying, in a very useful manner, its ulcerations. Delioux de Savignac, who took great interest in therapeutics, invented this process, and gave the following formula for an injection: Nitrate of silver from 0.25 gr. to 0.50 gr.; albuminous water 60 gr. To this, 120 gr. of tepid water were added, when desired for use. This is the only true way of using nitrate of silver in injections, owing to its faculty of being dissolved by albumen.

We can now understand how those albuminoid substances, which are found in such abundance in the digestive duct, are

able to dissolve calomel which penetrates into the organism as an albuminate of protochloride of mercury, and behaves like calomel. This likewise applies to protoiodide of mercury, to sulphur, phosphorus, and to all substances that are soluble in mucus and albuminoid bodies.

The digestive duct also contains large quantities of gases—sulphurretted hydrogen, and, in some cases, sulphide of ammonia. Of course, there is no oxygen, otherwise the sulphuretted hydrogen would be consumed. For a like reason, oxygen is never found in sulphuretted mineral waters. In some instances the intestine also contains nitrogen.

The sulphuretted hydrogen also causes changes in medicamental forms, when metallic salts, having gone through the first part of the digestive duct, reach the duodenum, and that portion of the lesser intestine in which there already exist fæcal matters. These saline substances may then be transformed into sulphides of iron, bismuth or zinc. This has its importance, because it is a way of neutralizing the effect of these active substances. Sulphides are very insoluble, and they pass through the digestive duct without causing any effects, since bodies only act when in a dissolved condition. But there is another important point. It is that the fæces reveal by their color when an excess of active principle has been introduced.

It is generally believed that considerable doses of iron are required to restore the globules and too much is almost always given. Thus, oxide of iron or reduced iron is always given, in doses of 0.50 gr. This is entirely too much. The same may be said of mineral waters when very strong, such as Spa, Orezza and Forges-les-Bains, which always leave an excess of iron, so that when a patient does not fully assimilate them, it is shown by the color of the stools. The physician, in such cases, reduces the dose of water to be taken.

Another peculiarity to be noticed is, that in a number of cases these sulphides are apt to deceive, when there exists a possibility of intestinal hemorrhages. Blood becomes black when altered by acids or by sulphuretted hydrogen. When substances of that

kind, producing a black sulphide, have been administered, it is sometimes difficult to tell whether a hemorrhage has taken place. Subnitrate of bismuth in diarrhœa blackens the fæces, which constitutes an objection to it when used in typhoid fever. For this reason I suggested giving oxide of zinc in place of the bismuth. It is a good absorbent of acids and gases, and can therefore render the same services. The oxide of zinc should, however, be associated with bicarbonate of soda, so that the acids from the stomach may be more speedily absorbed. For here is another difficulty—when oxide of zinc absorbs lactic or chlorhydric acids in the stomach. Chloride of zinc is then formed, which is a salt possessed of highly irritating, nauseating and emetic qualities. To avoid this I give it in large doses, because the larger the dose the less does this phenomenon show itself. It is only the neutral lactate which is nauseating. If you have a basic chloride enveloped in a mass of inert substance, you will not encounter the same objections. But when giving oxide of zinc with bicarbonate of soda, the same results are obtained as with subnitrate of bismuth, without the inconvenience of having black stools. Consequently this does away with the difficulty of discovering whether there has been an intestinal hemorrhage in diseases in which such an occurrence is possible.

CHAPTER XXII.

Albumen and the Alkaline Chlorides—Arsenic.

Albumen and the alkaline chlorides; rôle of Albumen in the economy; absence of certain chemical phenomena in the human organism.
Arsenic.

GENTLEMEN:

I have endeavored, in the concluding portion of the preceding lecture, to impress on your minds the importance of the albuminoid principles; I shall now demonstrate, or at least indicate to you, that albumen and the alkaline chlorides have the same dissolving action on medicaments, when introduced into the superficial or profound subcutaneous tissue, or when they are placed in contact with the denuded dermis.

Under these conditions the same phenomena which we have observed in the alimentary canal, when albuminoid principles were present, occur also when medicaments are placed in contact with the dermis denuded by a flying blister which has induced very little effusion; so that substances not notably soluble, such as calomel, oxide of gold, aurum redactum, or even oxide of iron, may thus become soluble through contact with albuminoid matters and alkaline chlorides present in the different regions where they are thus applied.

But it must be acknowledged that of all the parts of the body by which it is possible to introduce remedial agents, the stomach possesses the greatest power of absorption; for instance, albumen can form a soluble combination with alum, but solely if in presence of an acid; you can then very well understand that an albuminate of alum, insoluble of itself, becomes soluble in the stomach, that organ always containing an acid—phosphoric acid, according to some observers, lactic or hydrochloric, as affirmed by

others; the stomach must then be considered the most favorable organ for the introduction into the system of substances requiring special conditions to become soluble.

I have already demonstrated to you that albumen possesses the property of facilitating the dissolution of certain substances insoluble under ordinary conditions; but it possesses, also, another property, which might be expressed by saying that it acts as a suspending agent, hindering certain chemical phenomena which, without its presence, might occur; a moment ago I demonstrated to you that it aided the absorption of active principles; at present I will show you that this same albumen hinders these substances from undergoing modifications which, if it were not present, they would suffer.

Take, for example, the reaction of sulphate of iron with carbonate of soda; by double decomposition, an insoluble salt, the carbonate of the sesquioxide of iron, is formed, and this reaction has been brought forward as offering a possible explanation of the manner the ferric salts are utilized in the reparation of the blood corpuscles; for, it has been said, the sulphate of the peroxide of iron coming in contact in the blood with bicarbonate of soda there present, a double reaction takes place, that the carbonate was freed, the carbonic acid escaped, and that the remaining peroxide of iron, uniting with the globules, increased their redness; but this supposition, besides not sufficiently explaining the action of the ferric salts on the blood, is not even correct; for when the experiment is made in the laboratory, with an albuminous solution of bicarbonate of soda, no precipitation takes place.

Again, if to a solution containing silver, bromide of potash, and albumen, chloride of sodium is added, so as to form chloride of silver, you will not have any precipitation, the albumen present preventing its formation; even in the first solution precipitation might occur, but for the presence of albumen, which here again acts in opposing the realization of Berthollet's laws.

It may be objected that in such a solution there is no precipitate, because albumen acts as a dissolving agent, and though

chloride of silver is formed it is not precipitated; but here is another case where this objection is not tenable: lactate of iron is introduced into the circulation by direct injection, or by absorption; the attempt is then made to demonstrate its presence in the serum of the blood by means of ferrocyanide of potassium; some coloration should be produced, yet neither Prussian blue nor the French blue, which a protosalt of iron should give, is obtained; the absence of blue tinge shows that no Prussian blue has been formed; in other terms, that the new combination has not taken place; yet if acetic acid is added the blue tinge appears; the acid has simply modified the albuminoid principle, depriving it of its functions; for we already know that albumen, according to its modifications, may hinder, or, on the contrary, aid in, the speedy formation of combinations.

In photography, albuminoid plates are used, and without hindering the production of the reaction; but the albumen is dry, and not being modified, acts in opposition to the realization of a certain number of chemical phenomena observed when the albumen is in solution in a test-tube or watch-glass.

I have said that in the experiment mentioned above, if acetic acid is added the tinge of Prussian blue is obtained. Claude Bernard has taken advantage of this fact to demonstrate that the gastric juice is secreted solely in the superficial layers of the gastric mucous membrane, and not at the bottom of the glandular *culs-de-sac.*

After introducing lactate of iron into the circulation, he painted the internal aspect of the stomach with yellow ferrocyanide of potassium, and the blue tinge obtained was confined to the superficial layers of mucous membrane; showing clearly that the acid necessary in the presence of albumen for the production of this reaction was present only in these superficial layers.

These facts, as you see, are very curious, but may be considered as following certain general rules.

This action, suspending chemical phenomena which should occur, according to the laws of Berthollet (which laws have been more or less modified naturally since he first announced them),

this action, I repeat, is observed in the human organism and in the circulation; albumen will exercise its suspending properties on substances introduced into the blood and circulating in the serum of that fluid; thus preventing the manifestation of a certain number of chemical phenomena which would have occurred if it were not present. Take, for instance, this phenomenon, to which I have already alluded, of precipitation when a soluble body is introduced into the blood; thus a quinine salt, though an alkaloid, coming in contact in that fluid with carbonate of soda, is precipitated; as are also the salts formed by peroxide of iron. Now, if this precipitation really occurred, as Mialhe believed, what would happen? Why, just as long as these substances capable of causing precipitation appeared in the blood, emboli would be formed, which, being arrested in the capillary vessels, would induce dangerous accidents; and M. Mialhe considered even that the febrile state was modified in this manner by quinine, that the emboli thus formed penetrated in small particles into the capillary circulation, and thus acted in opposition to the phenomena of hæmatosis, which are the primary cause of the febrile state! But I again repeat that if such emboli were formed accidents would result analogous to those observed when tobacco seed or lycopodium in powder is introduced into the vessels of an animal. But there is yet another fact which would not be observed if chemical phenomena were affected in the blood as in the laboratory; the mineral acids introduced by the stomach to act on the blood, as when lemonade acidified with sulphuric or chlorhydric acids is given, the acid contained should combine with the soda of the blood to form sulphate or phosphate of soda, and consequently an excess of acid would never appear in the urine; and yet, though I concede that there is great difficulty, I consider it possible to modify the alkalinity of the urine, a state observed to be the normal condition for many persons not over robust, or affected with catarrh of the respiratory organs; but it is difficult to render such urine acid, and large doses are required.

Consequently, here are acids which pass in the free state

through the system to the kidney, and are excreted therefrom without change, which certainly would not happen if they came in contact with bicarbonate of soda in the free state, as in Vichy water, as phosphate of soda would be most certainly formed.

Pereira, whose work on therapeutics is classic in England, affirms that when hypochlorite of soda, known in France as Javel water, is introduced into the stomach, the urines carefully collected contain either free chlorine or hypochlorous acid, and that they even possess bleaching properties.

All these examples will serve to demonstrate to you that substances which, according to chemical laws, should combine with other substances existing in the blood, make the round of the circulation without being combined, and are found in the urine unchanged and capable of manifesting their peculiar properties.

But there are other facts equally interesting; certain substances eminently oxidable can make the round of the circulation without suffering oxidation; demonstrating that while in the blood they have not undergone the chemical transformation which their nature would seem to require, they have not entered into combination with the oxygen contained in the corpuscles of the blood, to pass to a higher state of oxidation; take, for instance, pyrogallic acid; there is no substance more void of oxygen, yet this acid has been introduced by Claude Bernard into the circulation, and has been found without alteration, and in the free state, in the urine of the animal. Here, again, we are obliged to recognize that combinations which, according to ordinary chemical laws, should occur, are impossible in the blood. Again, I will cite another instance, for these facts are many of them unknown, on account of their dissemination in many works; chloride of barium, introduced in a soluble state into the stomach, penetrates into the blood, there meeting with sulphate of soda; it should be immediately transformed into sulphate of barium, which, under ordinary circumstances, is formed with such facility that the salts of baryta are never found in natural mineral water, for they always pass to the state of sulphates and are consequently de-

posited in the earth; but this change, so facile as it is, does not occur in the human economy, and Woehler has shown that if chloride of barium is introduced, it is found unchanged in the secretions.

There are other very interesting experiments, but from which I drew, perhaps, somewhat exaggerated conclusions when I mentioned them, in 1867–68; these were the experiences of a chemist very well known through the observations he has made concerning the influence of iodide of potassium on the elimination from the system of metallic substances capable of inducing poisonous effects. Melsens has shown that when iodide of potassium is administered, it causes the metals to reënter the circulation. This I have demonstrated myself in a case of poisoning by arsenic; but this chemist has also occupied himself with a very interesting question, to determine what influence might be capable of inducing in the human economy the effects obtained by means of the most powerful agents in the laboratory, such as mechanical force, or electricity, by which, as every one knows, certain bodies can be formed or destroyed.

He took into consideration the question whether in the human organism the simple friction, the continual flow of the blood in the vessels, aided by a temperature of 37.5° C. in man, and of 42° C. in birds, would not suffice to determine phenomena analogous to those obtained in the laboratory by the powerful means mentioned above; he has arrived at affirmative conclusions on this question, and during his researches he has remarked a curious fact: if iodide of potassium is introduced, it produces the effects proper to it, and no others; the same statement is true of chlorate of potash, and either of these substances, given singly, are innocuous. Yet Melsens has demonstrated that these two substances, which do not react on each other in a test-tube, which remain as before, chlorate of potash and iodide of potassium, and which do not exchange the oxygen of the chloric acid with the iodine, except under certain determined conditions, when, for instance, the aid of electricity or mechanical force is brought into play; he has shown that these two substances make

this exchange in the human economy when both are introduced together into the stomach, and that toxic accidents, often proving mortal, even for pretty large animals, are induced. The fact is of itself interesting, but here are the conclusions I drew therefrom: I considered that if the two substances were introduced separately into the circulation, the one, for instance, by the stomach, the other by the rectum, that being absorbed apart from each other, and not coming in contact before arriving in the serum of the blood, they would not cause any fatal issue. I have not made the experiment, but I had considered it demonstrated by the following fact: large doses of chlorate of potash are given to a dog; then, three or four days after, large doses of iodide of potassium, and no bad effect is perceived. From this last experiment I concluded that, this animal having remaining in his system a certain proportion of chlorate of potash, not being poisoned by large doses of iodide of potassium introduced immediately after, these substances, under such circumstances, came in contact in the blood, but that no noxious effects were induced, because in this fluid they could not undergo the exchange necessary to the formation of iodate of potash, which is the only noxious salt.

But it might be objected that all the chlorate of potash had disappeared, or that, even when the iodide was given just immediately after the last dose of the chlorate, sufficient did not remain in the system for the formation of a notable quantity of the noxious iodate; consequently, opinion on the subject must be reserved; but I am convinced that, conducting the experiment as I have mentioned, so that each salt should arrive separately in the blood, no toxic effects will be induced; I will make the experiment, and in my course of lectures next year I will inform you if the results confirm the opinion I have expressed.

I have, then, shown you that a certain number of chemical phenomena are wanting. I will now demonstrate that certain substances which have very marked physiological effects are deprived of such action when in circulation in the blood; it will

be the most striking demonstration of the influence of albumen on the state of substances introduced into the system.

You all know what troublesome effects are induced by the application of a blister, too large, left too long in position, made up with more than usually powerful cantharides, or when applied on a surface which absorbs too rapidly, as over a part where dry cups have been applied.

You know that after a certain time painful symptoms supervene in the urinary organs, and that the active determination toward the kidneys and the bladder may cause the appearance of albumen, of fibrin, or even of blood in the urine, and this last in quantity so considerable that there results a large mass of coagulum, filling the urinary reservoir, which induces dysuria, not from oliguria, but by presenting an obstacle to the passage of the urine; I have seen individuals thus affected unable to urinate until the coagulum was dissolved; you are all acquainted with these phenomena, but not many have reflected concerning the manner of their production.

You observe an external surface absorbing a substance such as cantharidin; the vessels which absorb this cantharidin and which are filled with it must, at a certain moment, experience the toxic influence of the drug; there should be phlebitis and even plastic phlebitis to explain the presence of albumen and blood in the urine; very well; in the absorbing system of the region where the blister is applied there is nothing abnormal, and no one has observed a lymphangitis or a phlebitis in the parts about the blistered surface, although such grave symptoms of kidney trouble have been induced by the application.

How, then, can this be explained? Can it be considered that the quantity of cantharidin present in the kidneys was large, while in the general circulation it was in very small proportion? But no, there must have been as considerable a proportion in the vesicles which served to absorb it as in the kidney, consequently the facts cannot be thus explained; the true reason is the presence of albumen.

Albumen being present, opposes the accomplishment of the

physiological effects usually produced by cantharidin; but when, on the contrary, the drug arrives in the kidneys—that is, when it is eliminated in a secretion which normally is exempt from albumen—it becomes free, and produces on the kidneys, on the parenchyma of these organs, and on the rest of the urinary apparatus, the effects which cantharides ordinarily determines on the skin, on the mucous membranes, and on all the surfaces with which it comes in contact. Can you not see in this instance the most striking demonstration of the influence of albumen on the working of chemical affinities, and on the combining properties of remedial or toxic substances introduced into the circulation?

It can, then, be said to be a general law that albumen modifies remedial agents in a certain manner; that it aids in the dissolution of a certain number, rendering their introduction into the economy more facile; but once introduced, this same albumen opposes in the blood the effects, whether chemical or physiological, which these remedies usually exercise on the organs with which they come in contact.

That which I have just said may appear paradoxical, but the paradox of to-day may be a recognized truth to-morrow. Nevertheless, I do not go so far as to affirm that this influence of albumen is always absolutely or even generally exercised; there are facts which seem to indicate that it does not hinder the production of certain chemical phenomena; for instance, one of the exceptions that might be mentioned: I have said that urine normally alkaline might be rendered acid by administering the mineral acids; but I added, that to obtain this effect large doses were required, showing that a certain proportion must have combined with the bases with which they came in contact.

Sulphide of potassium is in part decomposed when introduced into the blood; sulphuretted hydrogen is liberated by the carbonic acid of the blood, and certain combinations take place, which may occur in the interior of the circulation, or, at least, during the passage of the drug through the system. There are, also, combustible substances which may be burned up and found in this state in the secretions.

I have shown you that pyrogallic acid may be found unchanged in the urine, and yet we know also that a certain number of substances introduced into the circulation undergo oxidation through the presence of oxygen in the blood, or in the tissues. Alcohol, notwithstanding the fine experiments of M. Perrin, cannot be collected entirely unchanged in the urine; when very large quantities of alcohol are introduced, there is a large quantity which escapes without undergoing chemical change; but when the quantity ingested has not been too large, there is production of aldehyde, or alcohol deprived of hydrogen, and there is another part which passes to the state of acetone, acetic acid, carbonic acid, or of water. The essential oils are similarly affected if spirits of turpentine be introduced; in the urine will be found a substance slightly oxidized, which gives to the urine the odor of violets, or a substance completely oxidized, a resin precipitable by nitric acid, will be collected; consequently the essential oils are partly oxidized in their passage through the system, but I cannot affirm that this takes place in the blood.

The alkaline salts are acted upon in the same manner. You are cognizant of Woehler's law; that any organic acid originating from the vegetable kingdom, when introduced into the system, enters into combination with potassa or soda, and is burned in the blood, and in the urine is found, not a citrate when citric acid is given, but a carbonate of soda. This offers an explanation of the *modus operandi* of the treatment of disease by fruit, grapes, cherries, or currants, which cause the urine to become alkaline, as do also the waters of Vichy and of Vals.

These facts have been reviewed and studied by Mialhe, who has rendered so many services to therapeutics and to physiology, and are now universally known. After the same manner, sulphide of potassium is excreted, in part, in the state of sulphate of potassa, that is, the sulphur has become sulphuric acid, and in this state has induced the formation of sulphate of potassa, which is thus excreted in the urine; consequently you perceive that in a certain number of instances chemical phenomena are not impossible in the human economy. I have, however, shown

you that they are accomplished with difficulty, being rendered difficult by the presence of albuminoid principles surrounding the substances in the blood.

I will continue the account of the chemical modifications possible in the human organism; compounds are split up, and copulation between compounds takes place; as you are as well acquainted with chemistry as myself, it will not be necessary for me to explain these terms. I have said that division of splitting up of compounds takes place; for instance, tannic acid splits up into gallic acid and glycol; it simply takes up water to add the necessary quantity of hydrogen and oxygen to that which it already contained. Again, copulation, or junction of different substances, is observed; there are a certain number of vegetable acids which, introduced into the circulation, issue therefrom as acids containing nitrogen, which they did not before contain, but they have encountered in their passage those substances, the glycocolls, to which M. Wurtz has called attention; they combine, they copulate with them and give birth to new acids; this takes place, for instance, for benzoic acid, which becomes hippuric acid; this happens also for the much talked of salicylic acid. There are a certain number of essential oils which in the same manner copulate with glycocoll, to pass in the urine in the state of acids containing nitrogen. You see, we have quite a number of chemical phenomena which occur in the living organism, and are not hindered by the presence of albuminoid matters. There occur also phenomena of reduction which are very interesting. It is difficult to understand that substances which enter the blood in the combined state and at a superior degree of oxidation, can in the organism lose a part of the oxygen they contain, for the inverse is the general rule; for substances introduced into the human system most frequently absorb oxygen and aid by their combustion to produce animal heat or muscular force; there exists, however, a certain number of substances which lose oxygen; thus, Woehler has long ago demonstrated that the red prussiate of potash, that is, the red cyanide of potash and iron (and which can be considered a cyanurate of potassium with peroxide of

hydrogen), is reduced to the state of yellow cyanide of potassium and iron; the demonstration of this fact is facile; the salt is introduced into the system, and if it passed unchanged, after treating chemically the urines, the addition of sulphate of protoxide of iron should produce French blue; but nothing is obtained under these conditions, and if sulphate of peroxide of iron is added Prussian blue is obtained, demonstrating that the red cyanide has lost its oxygen and has become yellow cyanide.

The same is true of the sulphate of peroxide of iron entering the system in this state; it is excreted as sulphate of the protoxide; that is, if you give a good quantity to a dog it will be necessary to add red cyanide to the urine to obtain French blue.

M. Rabuteau has encountered a similar experience: if seleniate of sodium is introduced, the selenic acid becomes selenious, a fact similar to that of M. Limousin, who observed that the protoxide of nitrogen could lose its oxygen and be transformed into nitrogen, which for a certain time might serve to keep up respiration and consequently preserve life.

But to these may be joined an entire series of hyperoxygenated substances, which Fourcroy had regarded as having considerable power, and whose number and importance he had, no doubt, exaggerated; I think, however, he was right in admitting that a certain number of suroxidized substances could yield atoms of oxygen; do I need to say that if he had known of the experiments of Claude Bernard, he would have considered them as aiding to prove his theory? But in his time the composition of many substances was not well known, or definitely settled. It has been remarked since, that chlorate of potash gave a scarlet tinge to the gums, as if a more active oxidation was being effected. Simpson, of Edinburgh, whose name is connected with the first application of chloroform to induce anæsthesia, employed chlorate of potash, convinced that it was a means of furnishing oxygen to the fœtus, when it seemed to him, by the presence of certain signs, that its circulation or respiration needed stimulation.

I have myself made analogous observations concerning the decomposition of chlorate of potash in the economy; I have caused

the analysis to be made of the urine of subjects to whom I was about to administer it; this analysis demonstrated the presence of a certain proportion of chlorides; then I administered the chlorate of potash, and found an augmentation in the quantity of the chlorides; consequently showing you that a portion of the chlorate of potash was decomposed, and that the chloric acid had lost its oxygen; analogous facts have been observed concerning other substances, and permanganate of potash has been thus administered to modify hæmatosis when it appeared insufficient. For the same reason, Dr. Simpson administered it in diabetes, when, as you know, the combustion is slow and not sufficient.

These facts are well established, yet they are still somewhat doubted by a certain number of physicians who have not sufficiently considered the mutations which chemical bodies may undergo in the economy. But all the changes that may be considered chemical take place elsewhere than in the blood; the vessels are but irrigating canals or roads which bear to the different organs the substances which they will be called on to employ; in the blood itself just a mere exchange of substances takes place, as in a railroad station the different cars are separately loaded; this metaphor will aid you in understanding what passes in the human system. Nevertheless, there are substances which really act while present in the blood, but they are gaseous or volatile bodies which act in the same manner as the air in respiration, directly on the blood corpuscles, and which accomplish their destiny, it might be said, in the blood itself; these substances I will cite to you; they are hydrogen, carbonated (carburetted) hydrogen, carbonic acid, and oxide of carbon, which spend their entire activity on the globules.

The same is true of protoxide or binoxide of nitrogen—substances which act in the circulation, as do, also, nitrous and hyponitrous acid; and prussic acid, too, acts in the blood, as do the nitrites of amyl and of ethyl, and all the volatile and gaseous substances which induce anæsthesia; as also the substances which nearly resemble them. These all induce phenomena

which really pass into the blood, and no more striking proof of this truth is needed than their instantaneous and often fugacious action, in the great proportion of cases. You are aware what passes when nitrite of amyl is inhaled; it enters the lungs and acts with astonishing rapidity. This instantaneous action demonstrates that it is in the blood that these substances have their action. This is what happens, also, in poisoning by sulphuretted hydrogen, which, in France, is called "*le plomb*," so named on account of the instantaneous nature of the accidents from it, the patients falling as if struck with a slung-shot (*plomb meurtrier*).

The same is true of the anæsthetic agents. You all know with what rapidity and violence they act. They have a double action: at first on the blood, then on the tissues; and this is true, also, of hyponitrous acid and binoxide of nitrogen; these are gases which act directly and with excessive violence on the blood, but, unhappily, their action is not instantaneous. If in a certain number of cases their action is very rapid, it is because the oxide of carbon or the nitrite of amyl penetrate very rapidly into the globules. They do not quit the globules so easily, but contract with the hæmoglobin combinations more or less stable, which cause the very dangerous nature of the accidents which ensue.

I repeat it, the instantaneity of their effects shows that these substances act directly on the blood, and, in effect, it is demonstrated, to-day, that prussic acid acts with such terrible violence simply because it enters into combination with the hæmoglobin of blood corpuscles, and hinders the incessant and necessary exchange between the atmospheric air and the different organs of the body, and thus prevents in the system the arrival of oxygen and the elimination of carbonic acid.

But in reality, with the exception of these volatile substances, all the other remedial or toxic agents act elsewhere than in the blood and not in this fluid itself. In the blood they are borne along side by side, and make the round of the circulation, without mixing, without acting, and without suffering notable modifications in their constitution or in their structure; exactly as on the same telegraphic line a great number of currents pass

and each traces a despatch on its arrival, without the least confusion.

These substances thus pass along unchanged in the blood, I repeat, because they are covered—as it were, encapsuled—in albumen, just as are the globules of buttermilk. If it were not so, these small particles of butter would unite to form one large mass on the surface of the milk, instead of remaining in emulsion. We know, to-day, that the existence of such a capsule prevents the junction of the globules and the formation of a mass; whipping the fluid acts by destroying this capsule.

These substances, which have thus made the round of the circulation, do not become permanently active, and do not suffer the modifications necessary at this point of view, before they become free, and this does not happen until they arrive in organs which do not contain albumen; then these substances become free, as in the urine, in the cerebro-spinal fluid, in the fluid contained in the internal ear, and in the aqueous humor of the eye, and here in these liquids there is a recurrence of symptoms due to the activity of the drug which had first induced notable effects on the surface to which it had been applied.

It is on this account, as I have already observed, that cantharidin circulates in the blood without manifesting its noxious properties; on its arrival in the kidneys, the urine not being albuminous, it acts on these organs as a veritable blister, renewing the effects it had produced on the skin.

There are also other phenomena observed when these substances, after being carried on in the blood, are exhaled into the liquids exempt from albumen, and thus come in contact with organs more or less sensitive; this explains why active substances like quinine induce such powerful effects on the auditory apparatus; it is because in these situations they can act with their entire power and induce, in this particular case, toxic effects on the peripheral extremities of the auditory nerves, whence the appearance of vertigo and that spontaneous affection called Menière's disease.

Several objections may be made against this view of the sub-

ject. It may be said that in the blood no effect is produced; that all the chemical phenomena occur elsewhere than in this fluid.

Claude Bernard has written that substances cannot act on the nervous centres, for instance, without having been introduced into the blood; in this fluid, he said, they produce their effects during their passage through the organs.

I think this opinion is not entirely clear, and furthermore, all the physiologists do not agree with the illustrious representative of the French school of physiology on this point; M. Vulpian does not admit that the phenomena induced by the alkaloids take place while these substances contained in the blood are passing through the organs; he admits, as I do, that these substances must arrive within the tissues of the organs themselves; that there must be parenchymatous intussusception, in order that there may be a more or less durable combination between the histological elements of the part to determine the modifications they are called upon to produce. To sum up, the true explanation appears to be that atropia, or morphia or strychnia, placed directly on the nervous centres, will not induce the usual phenomena which they are susceptible of producing, unless the drugs are first absorbed and then arrive later to act on the nervous centres; this fact does not, by any means, indicate that this effect is produced in the blood, but simply that the production of these effects is possible only through the exchange taking place between the blood and the organs, and solely when the substance which is to act as a remedy or a poison arrives in the organ at the same time with the plasma destined for its reparation. But it has been said, or it may be said, for I foresee these objections, that the toxic symptoms are often absent until, by an artificial process, such as the administration of the iodide of potassium, the substances are made to reënter the circulation in order to be again eliminated; for instance, take mercury, after a certain period, when there has been chronic poisoning; you will no longer observe the symptoms of stomatitis or of dyscrasia of the blood, which are among the prominent primary effects of the adminis-

tration of mercury, and which we seek to produce in secondary syphilitic affections. But if you cause this mercury to reënter the circulation, you may, in a certain number of cases, see the symptoms of stomatitis reappear, and, commenting on this fact, it has been said that mercury, while contained in the different organs, causes no toxic symptom, but when brought back into the circulation such accidents immediately reappear; yes, certain phenomena are produced, but no tremors or paralysis; it thus acts in a peculiar manner on the plasma of the blood; that is to say, that it is not impossible for substances to cause diverse phenomena while contained in the circulation; but the symptoms generally observed are those induced by the excretion of the drug.

It is the same for the other effects which may be produced by poisons returning into the circulation, after being disengaged from the tissues; symptoms induced by their excretion are always observed, but no phenomena of constitutional intoxication.

A third objection: the serum from a blistered surface, when it contains a large quantity of cantharidine, is capable of determining vesication.

I was not aware of this fact until recently, and this objection would not have presented itself to me, for I had not observed the fact before commencing to use M. Lailler's cantharidin collodion for blistering; this simply proves that when the quantity of cantharides is very large, and when the blisters act with great energy, there may remain a quantity of cantharidin in the free state.

Are you not well aware that there is an immense difference between an acid salt, and a strong basic or a neutral salt?

Do you not know that when a large quantity of acid is added to a sulphate there is free sulphuric acid? This is just what happens in the case of the blister, and although albumen has the power of hindering the action of substances when in excessive quantity, there is a part which becomes liberated.

To resume: it is no longer doubtful (what I have maintained so long commences to be recognized as a verity) that the great

part of the effects produced by active substances introduced as medicaments into the economy are not produced outside of the circulation; and that the albumen and the plasmin of the blood act only in a certain measure in opposition to the realization of chemical phenomena produced by active substances, and consequently do not entirely hinder the physiological effects which they may induce, since these last are obtained solely through physico-chemical transformations.

There is always, at least, a modification in the structure of parts when physiological effects are produced; for instance, sulphuric acid enters into combination with a tissue and deprives it of water; when it has effected cauterization, its composition is changed; it has become a hydrate. The same is true of chromic acid, and of potash, which combine with the tissues.

There are certain substances which only cede a part of their strength, as, for instance, the alkaloid of quinine, which is found almost unaltered in the urine, but is no longer quinine; it has produced exceedingly marked therapeutic effects (which were considered absolutely impossible when its therapeutic action in fevers was first spoken of); but when collected from the urine it has lost a part of its strength, and has become quinidia and quinicine. Then, whether substances suffer change or lose strength, the fact is certain, they cannot induce physiological effects without suffering some change in their composition or in their structure.

In order to complete the study of a molecule (as has been done of a crumb of bread), and to bring to light the various changes it suffers in the economy, it will be necessary for me to speak to you of the introduction of this molecule into the parenchyma of the different organs, of the duration of its sojourn, of its reabsorption, and of its elimination by the various emunctories.

But there exist difficulties in the demonstration of such a subject, which cannot be properly understood unless one has deeply studied these questions. On account of these difficulties I will demand your permission to take an example, and when by

particular care I shall have demonstrated to you the case of one particular drug, I am convinced that you will understand better the general laws governing the physiological effects which take place in all.

There exists a drug which presents itself naturally to us, on account of the interest it has excited in therapeutics, the high importance it has acquired in medical jurisprudence, and the researches made concerning it. I shall attempt, with the aid of this substance, to make you understand the modifications which medicaments suffer in the organism, and what temporary distributions they undergo. The substance of which I speak is *arsenic.* The subject itself is extremely interesting, and you all recall vividly the particulars of a case which has recently much moved the public mind.

I am of opinion that the history of arsenic, made in detail, will be useful to you; and I wish more particularly to present the subject to you, in order to associate the therapeutical and medico-legal sides of the question, and to thus inform you of a number of errors generally received concerning this drug, as also to lay before you a certain number of new facts; some belonging to myself, others collected from various observers, and which all give a peculiar interest to the question. We will then consider arsenic. The pharmaceutical form has little importance for this drug, and this is generally true of the minerals. When organic matters are to be used it is indispensable to introduce them in certain forms, and with the most perfect structural integrity obtainable, because they differ, often, one from the other, solely by loss of their dynamic properties. For mineral substances, on the contrary, the form under which they are introduced matters little; it is the mineral element contained that acts.

Arsenic, a metalloid, acting by itself, can be introduced in any form; the same formation of therapeutical phenomena will be observed, and the sole difference will be the aggravation or diminution of effects produced by different preparations.

Arsenic, it may be first laid down as a general fact, is a poison for

both kingdoms; it is a poison for all animals—there are none which escape its influence; but it is, also, a poison for the vegetable kingdom; a plant watered with it will perish. There is, however, one strange exception to this rule (the greatest criminals have friends); arsenic has for friend a plant unable to live except among substances containing this poison. There is developed in arsenical liquids a form of algæ which has particular characters, always the same; it is formed of bulbous articulations, in this respect somewhat resembling those of the mucedines of thrush; it is, if you will, a leptomitus, or rather a hygrocrocis. With this single exception, arsenic is, I repeat, a poison for all things possessing life, no matter to what kingdom they belong. It is an anti-zymotic or anti-ferment, as ferments are organic substances, even possessing an inferior degree of organization. But it is not sufficient to prove scientifically that a substance is an anti-ferment; it is necessary to know why it is so. This we know concerning certain substances, but why arsenic is antiseptic has not yet been determined.

What we do know is, that arsenic, which destroys the large organisms, destroys also the smaller, and even the globules; this explains readily a strange fact observed by those interested in medical jurisprudence: that in the bodies of those who have succumbed to the influence of arsenic the parts which have come in direct contact with the poison remain for weeks almost unchanged; the digestive organs are found in a state of remarkable integrity, while the rest of the body is in a state of putrefaction, an effect due to the antiseptic properties of arsenic.

It acts in the same way as an escharotic. I have just observed that it destroys the inferior organisms; it destroys also the histological elements of a part; it is not a caustic substance, but it produces a scar like a caustic; it does not produce an eschar by carbonizing the substance of an organ, or by transforming it into xantho-proteic acid, or into a soap; it kills it. I do not contend that it acts without producing any modification, but the part is not so profoundly modified as to be difficult of recognition.

In 1877, I repeated an experiment which I had also previously made; and which demonstrated that the eschar produced by arsenic contains the histological elements of the tissues; if in a muscular region, the muscular fibres are distinguishable, but they have lost somewhat; no striation is found when the part has contained voluntary muscles; when, on the contrary, the eschar has been produced by sulphuric acid, nothing remains but a magma without form, and no longer containing any trace of histological elements.

Arsenic, then, exerts simply a toxic influence on the part of the organism with which it comes in contact; it can no longer live, or if small doses have been used it lives under adverse conditions. This explains why arsenic as an escharotic has been regarded with so much favor; it seemed almost possessed of intelligence when it was observed how it attacked the different layers in the productions of new formation called cancers, and respected the neighboring healthy tissues.

Its intelligent discrimination in attacking tissues is, you understand, but a question of the proportion or quantity administered; when it comes in contact with a tissue well supplied with blood-vessels, it is partly carried off in the circulation, and there is never a sufficiently large quantity present to produce death of the part; in tissues not so well irrigated it is, on the contrary, apt to accumulate; it spares, then, the living tissues, but acts on the others when there is a great accumulation of new cells, as in encephaloid cancer. We will now consider the effects of this poison when it is placed in contact with the cutaneous surfaces, or when it is introduced into the stomach to pass from it into the circulation and thus enter the different tissues. When arsenic is placed in contact, in small quantity, with the skin, it determines a number of phenomena which are sometimes of considerable importance; for instance, redness, with sufficient heat to become disagreeable, is induced, and an eruption may ensue; when the intensity of its action is greater, this eruption consists in the development of *pimples;* the expression is not very scientific, but it nevertheless expresses the condition of things; a slight reaction

against the irritation determined by the arsenic takes place, and these pimples are the expression of the analogous inflammation which takes place to aid in the elimination of an eschar when produced by a caustic. But ulcerations may be produced if the quantity of arsenic is more considerable, and they may occur on the skin or on the mucous membranes; sometimes they are observed on the genital organs, where they produce a rounded ulcer, resembling somewhat the primary ulcer of syphilis. Similar ulcerations are met with in the noses of those who work at the manufacture of Schweinfurt's green (paint), and sometimes perforation of the nasal septum occurs, as happens from contact with chromic acid.

These phenomena are not observed during the therapeutical use of the drug, for a small quantity of arsenic is not thus diffused over the surface of the body, but they are often observed in workmen and in miners working in mines containing sulphide of arsenic, in those who manufacture Schweinfurt's green dye, and in the young women who manufacture flowers colored with this dye, a manufacture which has been prohibited by law; and such lesions were also observed to occur to ladies wearing these flowers. I have myself seen such results where it was the fashion to wear these brilliantly colored green leaves. These accidents have occurred also to those persons wearing or fabricating malachite, and they may be observed in a certain number of cases where rooms are papered with green paper containing arsenic.

But it must be admitted that the satined green papers have never poisoned anybody; but only the velvety papers colored by Schweinfurt's green, and containing fine molecules of the drug, applied on the paper with a sort of glue, constituting the velvet on its surface, thus coating the small solid particles of arsenic; it is easily understood that during the time the paper is dusted the currents of air carry through the atmosphere a more or less notable proportion of these molecules, which can be absorbed and determine the lesions they are capable of producing; and this does not happen, I repeat, with green satined papers, or with

curtains colored with this green dye. In a recent case, where the window curtains contained arsenical green dye, they were doubled with fine muslin, which should have contained a small proportion of arsenic if the green fabric had caused the accidents, yet Marsh's test failed to show the presence of arsenic.

Concerning this subject an interesting supposition has been proposed by a German experimenter; he thinks that when the curtains or wall papers of a room are colored by arsenical green dyes, in the confined atmosphere arseniuretted hydrogen may be formed; I think that there must be some mistake here, or, at least, that such is not generally the case.

For the production of arseniuretted hydrogen, certain conditions (of reduction) are necessary, which do not habitually exist in the rooms we inhabit; I have myself made known the possibility of the formation of arseniuretted hydrogen in arsenical mineral waters; it is sufficient to observe the disagreeable odor of these waters when in a state of putridity, to recall the odor of arseniuretted hydrogen burning in the air; that is to say, becoming oxidized. I called attention to this fact, explaining it by the reduction of the arsenic or arsenious acid (chemists admit that it is arseniate of soda), through their contact with the organic matters depositing in putrefying water; to-day I might possibly say, taking into consideration the experiments of Planchud, which demonstrate that an algous plant, the sulphuraria, is capable of decomposing sulphate of calcium, that algous growths favor the formation of arseniuretted hydrogen. But, whatever may be the theory, it is certain that in order to form, with arsenious acid, arseniuretted hydrogen, the presence of certain substances to favor oxidation are necessary, which are not present under the conditions in which we usually live; I contend, then, that it is not usual to encounter arseniuretted hydrogen in rooms where green wall papers are present.

We can now consider the action of arsenic on the digestive organs; and here we will have to distinguish between the topical effect, the reflex phenomena, and the general or diffused effects of the drug, as we always do in studying a therapeutic agent.

We will first consider its topical or local action; and this is very interesting as recalling a general physiological law, which is, that the drug produces different effects according to the surfaces with which it comes in contact. This shows that we resist the action of the drug, and that each organ reacts after a certain fashion proper to itself, and thus induces different impressions and sensations; as, for instance, when arsenic is introduced into the nasal passages, it induces sneezing, by the sensation it determines on the parts; placed in the mouth, gustatory sensations are experienced; a metallic taste when there is a very small quantity, and when the dose is large, a burning, acrid sensation is induced in the throat; and it is here that its topical influence is most considerable; the same feeling is experienced in the pharynx and œsophagus when the poison descends.

The substance arrives finally in the stomach; what feeling will it there induce? Certainly no sensation of taste will be experienced; the stomach is the seat of the sensation of desire for food, or appetite, and it is this sensation which is developed when the quantity of arsenic is small; in other terms, the trifling sensation determined by the arsenic in the stomach causes the production of a desire for food, which is a normal sensation when proceeding from that organ. Naturally, if a more considerable quantity is ingested, symptoms induced by irritation, as sensations of heat, and of more or less burning pain, are experienced; then other phenomena succeed, such as dyspepsia, with pain and consequently gastralgia, and if the dose has been still larger the individuals suffer from nausea, followed by vomiting, which almost always happens; these are the most characteristic phenomena of the action of arsenic.

But I am obliged to observe to you that this symptom is not constant, and that there have been cases where arsenic was ingested in such proportions that death ensued, and yet where vomiting never occurred, nor any of the symptoms of arsenical poisoning. You will find such cases mentioned by authors of great weight on this subject, and particularly by Taylor.

Vomiting is, in fact, the result of an impression made on the

peripheral extremities of the pneumogastric, and is not determined necessarily by the irritation, or inflammation, or even by the ulceration of the stomach—all grave lesions of the organ.

The emesis produced by arsenic is identical with that induced by tartar emetic, or ipecac; there is a particular excitation which may be followed or not by its effects; the excitation, even, may not be present, as paralysis of sensation, or even of motion, may occur in the interior organs, just as in the peripheral organs, and for the organs connected with nutrition of the organism just as for those connected with the functions of relation. There are cases where the stomach is devoid of feeling, and others in which, though common sensibility be present, there is not sufficient reaction to produce emesis; this happens in certain pathological states.

I will defy you to produce emesis in subjects in a low typhoid state, where pulmonary congestion is diagnosed, and where it would be advantageous. I have never succeeded; and why is this so? Because, perhaps, common sensation is wanting, and to produce emesis the coöperation of all the thoracic and abdominal powers are necessary, and besides the contractility of the stomach itself, complete integrity of the nervous system and of the organs are necessary; and though these conditions may exist at the moment the poison is introduced, they may disappear through the state of prostration in which it throws the subject; this is the reason why no vomiting is observed in some cases, though the drug may have caused death.

Besides these symptoms and the phenomena which accompany them, there are others due to the irritation which the poison produces in its passage from the stomach to the end of the digestive tube. This irritation causes various changes, according to the intensity of the action of the poison; sometimes simple redness, at other times extremely marked redness, with ecchymotic spots, even inflammation, with softening of the mucous lining; and, finally, if the patient has survived longer, ulcerations, left after the elimination of eschars. You see, then, that according to the period at which the examination is made, and

the quantity of the poison ingested, you will have different phenomena.

The reflex phenomena determined by inflammatory action supervene later, but these do not show that absorption has taken place, and you will see that it is indispensable to distinguish the lesions produced by sympathy from those supervening after the diffusion of the drug, on account of the great importance such discrimination may present in a medico-legal point of view. The modifications produced on the stomach are of no consequence, unless the sensibility of the organ is intact and it has the necessary power for the production of emesis. As I have just said, there are cases where no emesis takes place, and if, under the influence of arsenious acid, symptoms of collapse are produced, following its absorption and not preceded by reaction of the system, you may witness the evolution of all the symptoms of poisoning without any of the characteristic signs, such as nausea, vomiting and alvine evacuations. I have just observed that if the effects do not prove immediately of so much gravity, there are more or less marked symptoms of irritation, and, as post-mortem examination has shown, softening may be found, more or less circumscribed, in different points, and even ulcerations, when these softened points (this change being analogous to the formation of an eschar on the periphery) have been eliminated.

At the same time that these effects are produced there is a repetition of the efforts to vomit, or, perhaps, oftener, to go to stool, and a profuse diarrhœa is observed to come on, with repeated evacuations of matter, which varies according to the period at which the affection has arrived.

At first, fecal matters, simply softened, are ejected; then serous matters, and even rice-water discharges, and, finally, phenomena resembling those seen in dysentery are observed, which coexist with or are induced by the ulceration of the stomach and intestines; pure blood and matter resembling coffee grounds are passed, as in simple ulcer. Such are the phenomena which arsenic determines in this portion of the digestive tract. But

there are other general phenomena induced through the influence of these local changes on the entire system; these are called sympathetic or reflex.

It is not possible that such disorders be produced in the mucous membrane of the stomach and intestines without inducing choleriform symptoms, which, as you know, exist in all cases of poisoning by acrid substances. You will observe that subjects presenting such lesions offer the following symptoms: the face is haggard, the eyes often appear sunken, a black circle is traced under the eyelids, and the face is more or less pallid; this appearance has been considered a necessary adjunct in cases of poisoning, but it is observed solely when these grave lesions have been produced; otherwise, when the lesions are not marked, nothing similar has been observed. Next, haggard face, prostration, loss of strength, and at the same time, profound troubles of the various functions—respiration becoming difficult, the patient feeling a weight oppressing him, with disorders of the circulation—the pulse becomes small and thready, later it becomes slower, then the sense of frigidity, at first local, becomes general, the nails are cyanosed; then you see suppression of the urinary secretion ensue, as in cholera; but these phenomena are observed in every case of poisoning, and afford no indication of the nature of the poison. If sulphuric acid is introduced into the stomach, those same choleriform symptoms ensue which are observed after all lesions affecting the digestive tube or the innervation of the pneumogastric.

There are other very singular phenomena occurring at this period; convulsions and spasms are observed, and true tetanic symptoms may supervene. Tetanus is, as you know, a very grave affection which sometimes occurs as a complication in lesions of the extremities and of the abdomen, for other traumatisms are much less frequently followed by its appearance. This is a very curious fact; and often when ovariotomy has been performed, the women succumb to tetanic spasms; this fact might find an explanation in the existence at the periphery, in the extremities, and in the abdomen also, of corpuscles of Pacini,

which are more numerous under the peritoneum than elsewhere; whether this be the true explanation or not, it seems to me an interesting anatomical fact to mention.

Now, after having spoken concerning the local action and concerning the effects induced in the general system by sympathy, I will consider the action of the drug when diffused in the organism. I will study separately the effects as induced by small, moderate, and large doses. As relates to small doses, they are generally not very offensive in their effects; they are introduced for the hygienic or therapeutic action ascribed to small doses. You all know the account given by Tschudy of the toxicophagi, or rather, arsenicophagi, inhabitants of Styria, of Carniola, and of lower Austria, who imitate the custom of horse sellers, and in order to improve their personal appearance and give themselves certain qualities wanting in their race, are accustomed to take more or less considerable doses of arsenic, or rather, of arsenious acid.

I have placed these facts under the category of small doses, for they take small doses, as 1 or 2 centigrams (one-fourth of a grain) per diem, augmenting gradually the dose; the picture traced by the observers of these individuals appears to me too flattering; it is said that they acquire great strength, have remarkable agility, climbing the steepest mountain sides; while they were easily put out of breath before taking arsenic; in fact, they are said to feel like flying, as they express it themselves; as for the young girls, they become veritable rose-buds, as colored as ripened apples; they acquire flesh even; and as fine skin is never seen in thin people, over bones thinly covered, their skin becomes clearer and more transparent. But, unfortunately, there is a dark side to the picture; arsenic does not always give such admirable results, and when these individuals come to require considerable doses serious effects may ensue; so much so, that Tschudy, the great panegyrist of this habit, avows that a certain number of subjects become sick and end in marasmus; he considers that such persons have not properly taken the drug; but it is certain that many lose flesh and that some are affected with

paralysis, due to the action of the poison; this happens rarely, it is true, for generally they possess sufficient sense not to take large enough doses to induce such noxious effects. But I wish to inform you that five or ten centigrams (from three-fourths to one and a half grains) cannot be taken day after day with impunity, or without producing evil effects, although such has been asserted to be the case.

I come now to the uses of the drug in therapeutics; and I will first speak concerning the small doses which we generally give, such as from five and ten milligrams to five or ten centigrams; when these doses are employed no great effect is at first perceived; perhaps a slight increase of appetite, and in certain cases slight thirst, are experienced, but no phenomena induced by the diffusion of the drug through the system; but when these doses are repeatedly given, for a considerable time, then the effects are marked, and particularly in morbid conditions.

You are aware that in the physiological state the economy is possessed of so much elasticity that it does not obey or is not easily affected by substances introduced; while, when there is a more or less diseased condition, the morbid phenomena which a poison or medicament is capable of producing are manifested in full force. When patients are in a febrile state, as in tuberculosis, the following phenomena are observed when arsenic is taken: a falling of the temperature has been mentioned; it has been observed, and to a notable degree, but it is not accompanied by a marked descent of the mercury, as happens after the administration of such substances as quinine or digitalis. Nevertheless, there is a slight reduction of the temperature, but it is only when large doses are introduced, or when there is chronic poisoning by arsenic, that very notable diminution of the temperature is observed; moderate doses reduce the temperature perhaps one-half or one degree. There is also a diminution in the number of pulsations, and this is well marked in phthisical patients; some sedation of the heart is produced, not only in the number, but also there is diminution in the violence of its contractions, and this diminution of the intensity of the contrac-

tions is so considerable that they become normal, and the impulse felt at the apex is much less violent.

These facts are indubitable to-day. Even when there is no fever the action of the heart may be moderated under the influence of arsenic. Furthermore, when careful examination is made it will be found that a diminution of the quantity of urea coincides with the fall of temperature. It has even been advanced that there is a diminution at the same time of carbonic acid; that is, that the quantity of urea which is at the highest state of oxidation to which nitrogenized matters can arrive is reduced at the same time with carbonic acid, which is the last term of oxidation of ternary bodies; consequently there would be a diminution in the burning up or oxidation in the system of combustible matters, no matter what they may be.

To resume, you can see of what importance arsenic may become, particularly if this last property be admitted; for if it were absolutely demonstrated, it is evident that there would be, after its administration, a reduction in the combustion going on in the system.

But because there may be a diminution in the quantity of urea excreted, we must not too hastily conclude that there is reduction of the entire combustion going on in the system; there may be an increase in the combustion of ternary substances. But if we had also a diminution in the quantity of carbonic acid, the fact would be proved. Under the present condition of science on the subject, it may be said that there is a reduction of functional activity of all the great organs, and not only that there is diminution of the combustion, but also a reduction of the activity of tissue formation and decomposition or absorption, and hence reduction of temperature. When phthisical patients are under the influence of a febrile state, caused and kept up by the existence of localized lesions, if arsenic is administered there is diminution of fever and possibility at the same time of amelioration, since there is less active denutrition through the lessening of the febrile symptoms.

To return to our consideration of the toxicophagi, or arsenic

eaters, I think that the individuals benefited by arsenic are those generally who have slight fever, such as chlorotic patients (*febris alba virginum*), with whom it is sufficient to arrest excessive denutrition and exaggerated combustion; and this is exactly the effect produced by arsenic when it improves the personal appearance of subjects who are in the condition I have mentioned.

This is the opinion I have always held and defended: that arsenic is an agent which has a sedative effect on all the phenomena of hæmatosis, of respiration, combustion, and also on those phenomena induced by morbid irritation in pathological states.

This is not the opinion which has been always held, even in this school; thus, in 1865 the opposite opinion was maintained, in a long article on asthma,* and it was founded on a small number of experiments made in foreign schools, where, under the influence of arsenious acid, a diminution of carbonic acid had been observed; this conviction had become an article of faith with some persons, and it was said that arsenious acid augments the combustion in the system, and thus increases the state of denutrition, or decomposition, as also of formation or composition of the tissues, and that through this exaggerated condition of renovation the body renewed itself; to-day this opinion is no longer considered of any value.

Now we come to the consideration of moderate doses—of one, two, or three centigrams. These are doses often given in intermittent fever. Thus Boudin, and all that school which made more or less use of arsenic, often gave up to five centigrams in intermittent fever, and I believe it is the sole method of efficaciously combating this fever with this drug; as for the other febrile states, such as are observed in phthisical patients, they are moderated by smaller doses.

But when it is necessary to treat the intense attacks of fever caused by miasmatic influence, of so much gravity as those

* Germane Sée: "Nouveau Dictionnaire de Medécine et Chirurgie Pratiques." Paris, 1865. Article, "Asthma;" 3d vol., p. 583.

treated by Boudin in Algeria, then small doses have little effect, and it is necessary to prescribe almost toxic doses, producing the state of collapse, of which I have spoken, and inducing accidents more or less approaching the choleriform symptoms.

I confess, I have not had any success, for I am not one of those who give large doses of arsenic, except in one single case, where a somewhat large dose had been administered; the patient fell into a state of prostration, which I had not desired to produce, but from which he profited. We will then consider doses of one, two, or three centigrams. With the exception of a few symptoms of intolerance, which are manifested in delicate subjects, the same phenomena which I have already described occur in the circulatory system; generally, there is a tendency to reduction of temperature, but insufficient when it is necessary to act on an access of fever of any gravity. But certain other phenomena, those of elimination, are observed also, which do not appear after small doses. So that there are not many symptoms of trouble in the digestive organs—a slight intolerance; no troubles of the general system; but when these doses are continued, phenomena induced by elimination from the emunctories ensue; and these last may exist after very feeble doses, but are more marked when the moderate doses of which I now speak are taken.

A small quantity of arsenic induces, very often, marked diuresis, a veritable hydro-diuresis, just as is induced by acetate of potash. In a certain number of cases the contrary effect is produced; the quantity of urine is lessened, there is oliguria, and you will be able to recognize beforehand what will ensue. I have given you the general rule: In all cases where the kidney is in the normal condition, and is not congested, if a substance capable of exciting the circulation is injected into it this excitation shows itself by an increase in the quantity of the urine.

When, however, the organ is in a congested state, and there is already considerable passive tension, if the same substance which just now caused diuresis is introduced, it increases the intensity of the hyperæmia, which may have been on the border of actual inflammation. Veritable phlogosis is thus produced, and partial

and even complete suppression of urine ensues. This fact should be remembered.

In the liver, analogous symptoms have been observed; in certain cases, after sensations of malaise and of plethora in this region, bilious diarrhœa is observed; it is the arsenic passing by the liver and causing irritation. Similar phenomena are observed on the integuments; eruptions more or less marked occur on the skin, and under varying forms; sometimes it is simply irritation, provoking itching; then, again, small pimples or vesicles are observed. Then, when it is a chronic skin affection that it is desirable to modify by arsenic, a grayish tinge, on which M. Hardy has insisted, is observed. This tinge seems to be the result of an exaggerated deposit of pigment, but it is really due to the deposit of the metallic substance, as in poisoning by silver or lead. Sometimes a veritable erythema is produced.

This same effect, which shows itself on the skin by the lesions I have mentioned, is manifested by somewhat similar troubles on the eyelids. There is redness and an exaggerated secretion from the glands of Meibomius; the eye itself is sometimes congested, as in this region there is always a tendency to the exhalation of serous liquid in the interstices of the cellular tissue whenever any morbid condition is present; œdema palpebrarum occurs, as it does in all the inflammations of the eyelids or eye. The œdema arsenicalis is, then, nothing peculiar under these conditions.

The mouth is similarly affected. Eruptions are not seen, as on the skin; they are modified on mucous membranes, on account of the anatomical differences between the parts; but sub-inflammatory states, with exaggerated secretions, and in certain subjects, salivation, even, may ensue.

In cases where toxic doses have been taken such abundant salivation has been observed, and accompanied with a certain degree of gingivitis, that those who have witnessed it have been often mistaken, and considered it as a case of mercurial stomatitis, and with greater show of reason, the secretion, etc., being extremely fetid. This is a fact which I desire to call to your attention; we

are accustomed to see mercurial stomatitis accompanied by so repelling an odor that it is difficult to approach the patients. But how is this odor produced? It is not caused by the condition of the mouth, nor by the animal substances submitted to the influence of the saliva; there must then be some peculiar matter present, perhaps some compound in which the metal has its part, and which is constituted by one of the numerous radical bodies with which we meet so often in the combinations of organic substances; this same phenomenon takes place with arsenic and with lead.

I come now to the consideration of large or toxic doses; and the doses are of this character when they approach or reach five centigrams. As I have already told you, accidents ensued when these doses were given in intermittent fever; and, in effect, when the above dose is exceeded grave accidents may supervene; first, there is exaggeration of all the phenomena which you now know to be produced by arsenic; then more or less severe pains are experienced in the limbs, and tremors, convulsions, convulsive twitchings, and even, sometimes, tetanic contractions may be observed. The trouble in the nervous centres is manifested by symptoms of excitation, by delirium; and this delirium may be intense, lasting, not hours, but days and even weeks, and compromising existence, for death may ensue, just as in an ordinary inflammation of the meningeal coverings of the brain.

Sometimes opposite symptoms appear; want of sensibility in the muscles, and paresis, and even veritable paralysis, may come on; and then, instead of the delirium, coma may be observed; or sometimes delirium and coma alternately, and death arrives while the patient is thus suffering. I will not return to the consideration of the reflex phenomena, for they are present when moderate doses were used; but in conjunction with them the grave troubles I have just mentioned occur when large doses are administered, and then only.

One word on paralysis of arsenical origin; and here again the subject is very interesting; it can be affirmed that to-day the history of arsenic presents a great number of new facts, which, if well known, would render the opinions of experts in medical

jurisprudence much more reserved in the interpretation of cases submitted to them. I affirm, then, that arsenical paralysis exists, and I made mention of the fact in considering the hygienic use, in small doses, of the drug.

These facts occur commonly enough, taking into consideration that arsenical poisoning is not an every-day occurrence; they are not, however, often published. Nevertheless, M. Hipp Barella,* physician in the vicinity of Namur, has been able to collect twenty-nine cases; and these facts are known only since the eighteenth century; yet a certain number of authors, and among others my respected colleague, M. Jaccoud, seem to doubt the existence of paralysis of arsenical origin. But it certainly exists, for I have observed its occurrence in a case of voluntary arsenical poisoning. A woman, having many causes of anxiety of mind, poisoned herself with about a coffee-spoonful of arsenious acid, that is, with about seven or eight grams; the symptoms which ensued were formidable, and she seemed several times about to succumb, but I saved her, or rather aided in her recovery, and she enjoyed tolerable health afterward. Very well; in her case there was paralysis of all the four limbs, resembling very much saturnine palsy; but afterwards, instead of the flaccidity observed in lead palsy, there was a sort of retraction of the flexor muscles, which were not paralyzed, while the extensors were affected in just the same order as when caused by lead poisoning; and the forms of paralysis are so nearly identical that, one day, when Duchenne, of Boulogne, was in my service, I indicated the patient to him as a very interesting case of lead palsy; he examined her with care, by electricity, and returned to me saying: "Yes, it is a fine case of saturnine paralysis," and was very much astonished when I informed him it was not. Christison has remarked that arsenical paralysis very much resembles lead palsy. I consider that in some cases the two forms of paralysis may be identical.

You can easily see that this is a very interesting phenomenon, for it shows that there are general laws in pathology, as in thera-

* Barella, de l'emploi therapeutique de l'arsenic. New edition. Brussels, 1866.

peutics, and that if certain muscles and certain collections of muscles are affected by lead, it is not because lead acts specially on them, but because there is a predisposition in certain muscles to be modified by all foreign substances acting on the nervous system. There are muscles predestinated to these forms of paralysis; and it is a remarkable fact, to which I called attention twenty-five years ago, that it is the extensor muscles which are always affected in convulsions or paralysis; they are the most easily influenced. The flexor muscles, on the contrary, resist more; not only are they not easily paralyzed, but it is difficult to induce convulsions in them; you have remarked that in tetanus it is always the extensor muscles which are contracted; and when we reflect, the extensor muscles are the most feeble; both anatomy and physiology demonstrate this to be the fact. During the evolution of the new being the body of the fœtus is drawn together, or flexed upon itself; and during intra-uterine life it is the strongest muscles which come into play; and these muscles are not so easily affected by toxic agents; they are not so easily convulsed or paralyzed as the others.

A very interesting point in the history of the various medicaments, which concerns therapeutics and also medical jurisprudence, is to know whether arsenic accumulates in the organism; some observers say yes; others, no. I consider that it depends very much on the condition of the subject to whom it is given; in certain conditions there will be accumulation of doses and of action also, while under other and opposite conditions of the system this accumulation will not take place. What, then, are these conditions? When the subject is in good health, and has been surprised in good conditions of the system, when, also, the kidneys are normal, there is no accumulation. And this is easily understood; the valve is open, the kidney is ready for the issue of foreign matters, the filter allows almost all the substances entering it to pass. If, then, no doses large enough to prove speedily fatal are introduced, there is a possibility that not the least accumulation will take place, and that just as the substance enters, so it will be excreted by the various emunctories.

Suppose a case under opposite conditions—kidneys which do not perform their functions properly; suppose a subject affected with interstitial or parenchymatous nephritis, or a diseased state of the kidneys from the presence of amyloid matters. This subject will be delivered over to a poison which he cannot rid himself of; the urine is in small quantity, and will not possess the power of eliminating the poison. Here, then, are exactly contrary conditions, and in which different and contrary phenomena will take place. Now, will there be accumulation? What does the expression signify? A distinction has been made between the accumulation of action and the accumulation of doses. I believe that both amount to the same thing in the end. Accumulation of doses signifies that there is accumulation of the substance in the (primæ viæ) digestive organs, as happens with strychnine pills, which do not dissolve readily, but some day dissolve all together, producing symptoms of more or less gravity. Accumulation of action—which signifies that the medicament passes into the parenchyma of the different organs and accumulates there—and the quantity taken up by the work of absorption and eliminated not approaching sufficiently the quantity of the substance ingested, there ensues accumulation in the histological elements of the tissues. But, as you can readily see, there is always accumulation of doses or quantity.

For how long a period does the elimination of arsenic last? Another very important point for consideration. It is clear that if the drug is administered constantly this period may be indefinite; but, naturally, we suppose that the important point is the duration of the elimination after its administration has been stopped, or after one very large dose has been taken; concerning this point there is great divergency of opinion among different observers; a certain number believe in a too rapid elimination, and consider that the arsenic has disappeared after fifteen or eighteen days; there are others who think that at least a month is necessary; Chatin and Orfila are of this opinion. I go beyond even this period; in the case of which I have spoken—where the patient had probably taken eight grams of arsenious

acid—the suicidal act occurred on September 25th, 1864; the woman entered my service October 23d, that is, the following month; on the 27th I caused an analysis to be made which showed a large quantity of arsenic in the urine; consequently, as you see, that was thirty-two days after the poisoning. Another analysis was made thirteen days later, and arsenic was still found; consequently, I can assert that during forty-five days arsenic was eliminated in the urine. Nevertheless, on November 10th, another analysis was made, without revealing any traces of arsenic; then recalling the experiments of Natalis Guillot, and Melsens, on November 15th or 16th I gave iodide of potassium, and then on the 19th another examination of the urine was made and a considerable quantity of arsenic found to be present; and very moderate doses of iodide sufficed to bring this about.

But this woman had presented symptoms which had their seat in the encephalic nervous centres, delirium alternating with prostration, and I found myself obliged to shave the head and make cold applications. Her hair grew again, and I thought, after a certain number of months, that it would be curious to know if the hair contained arsenic. The analysis of the hair, made eight months after the poisoning, gave a quantity of arsenic sufficiently considerable; and this fact has great medico-legal importance, for the hair is not destroyed after death; as proof, you need but regard the hair on mummies, and consider the length of time it is thus preserved; so that even after a century arsenic could be found in the hair of a person poisoned with any considerable dose of the drug.

CHAPTER XXIII.

Arsenic (Continued).

Its passage through the system; rôle of the liver; plasma; histological elements.
Topography of arsenic in toxicology; death by arsenic.

GENTLEMEN:

Now that we have seen arsenic enter the system by different channels, and leave it more or less modified; it remains for us to know what organs it has traversed and what route it has followed, after entering the organism.

We will, then, attempt to follow step by step in its progress, the arsenic introduced into the digestive organs, which is its usual entrance.

Arsenic is first taken up by all the vessels, of whatever description, which belong to the digestive tube. It is taken up by the lymphatics, by the portal venous system, and is found naturally in the ante-hepatic or cis-hepatic vascular apparatus; but from the digestive organs it is particularly carried off by the radicles of the portal vein.

It encounters, in its passage, the liver, an enormous gland, which has, in my opinion, a similar action, with relation to poisons introduced into the digestive organs, to that exercised by the lymphatic glands on poisons introduced through another channel.

You know what Ricord has learned in relation to the buboes which are produced successively in the vicinity of the primary sore.

These buboes arrest the specific pus in its passage, and it is even true that if they are opened and cauterized there is a possibility that ulterior general infection may not ensue, the specific

poison having been arrested in the nearest collection of lymphatics.

You can, perhaps, call to mind the recent researches of M. Colin, of Alfort, who has demonstrated that the glands placed on the passage from the primitive lesion of malignant pustule (le charbon) arrest the specific matter peculiar to this disease once, twice, three times, and they always oppose a new obstacle to its introduction into the general system. Very well; in my opinion, the liver acts in a similar manner, and like these glands, arrests in their passage toxic substances introduced, accidentally or with criminal intent, into the digestive organs.

We will see later on in what manner the liver is thus enabled to arrest these substances, and in what part of the gland arsenic and the other poisons are arrested.

Arsenic, then, enters the blood vessels and is carried into the general circulation. How does it act when thus contained in the blood? We observe, first, the great general fact on which I insist, that arsenic, like other substances foreign to the economy, is primarily incarcerated in the plasma and in the albumen, and has very little activity while in circulation in the blood. Nevertheless, I have said that opinion on this subject should be somewhat reserved, and I have shown you that when the quantity of the noxious principle was very considerable, and in too large proportion to be completely neutralized by the plasma, a part remained in the free state just exactly as acid in excess in a salt will have the same action as free acid.

Something similar takes place for these more or less unstable combinations into which noxious principles enter with albumen.

I have shown you that cantharidin, having passed into the serum of a blister, could act again on the skin of another region in the same individual, or even on the skin of another; but the quantity of cantharidin must be enormous to have these effects. Very well; a similar phenomenon takes place in the circulation; when the quantity of the active principle is very considerable, it may produce toxic effects even while contained in the interior of the organs of circulation.

And as for arsenic, it is admitted that while in the circulation it may contract with the hæmoglobin a combination similar to those into which it enters with the noxious principles, and that this action on the globules may show itself by phenomena of sedation and of diminution of hæmatosis.

There result, then, symptoms showing a lessening in the performance of the duties which these globules are called on to produce. We get a better comprehension of this action of arsenic, by comparing it to that it exercises on the inferior organisms regarded as ferments. The globules can be compared to these protococci, and are similarly influenced by toxic substances; so arsenic acts on them in a way to prevent them performing their functions. But there is a third stage: arsenic quits the vessels with the plasma, to penetrate into the histological elements and here have a new action.

What effect does it have in this new situation? Formerly it was considered sufficient to say, according to chemical analysis (this opinion dates particularly from the beautiful experiments of Orfila), that arsenic was stored up in a certain number of organs, and particularly in the liver; and for a number of years the liver alone attracted attention in this relation. This was called a storing up, a condensation. The question is to know how arsenic is thus stored up or deposited in the liver, and how this gland happens to contain, in general, a considerable proportion, while there is little elsewhere.

It was not discussed whether cavities existed in which the poisonous substance was thus condensed or collected, or whether the deposit occurred in the vascular system, in the lymphatics, or in the parenchymatous cells. It is very probable that arsenic, like the other poisons, is stored up in the lymphatic plexuses of the liver, and also in the cellular elements which constitute the secreting cells; those which take from the blood certain materials which are restored again to this fluid, but solely after having remained a certain time accumulated in these cells. That is to say, that it is not simply an apparatus through which the blood passes, and which then excretes a serous fluid more or less

charged with principles to be eliminated; no; these are cellular divisions, composed of voluminous cells, in which the principles ulteriorly destined to constitute the bile enter and remain a greater or less length of time.

When you examine the hepatic cells in a normal liver, and more particularly when there has existed any obstacle to the circulation, you will find these cells more or less distended with biliary matters; that is, biliary pigment. It is by dehiscence, irregular, it is true, that these products, which have been accumulated during a greater or less length of time in the parenchymatous cells, are poured into the biliary canaliculi, to be transmitted thence into the more voluminous canals, and thence again into the gall bladder and intestine.

I mention this to you in order that you may understand how it happens that poisons entering the liver remain there longer than in the other organs of secretion, and in particular, longer than in the kidney. They pass through the kidney without any delay; but they sojourn in the liver, for it is only by a sort of dehiscence that they are poured into the excreting canals.

You can now easily understand how the quantity of the noxious principle is so considerable in the hepatic gland.

How does this happen? It may be thought that it simply penetrates into the intercellular substance in somewhat the same manner as iodine into starch. For you know that the iodide of starch is not a chemical combination; the iodine infiltrates into the interstices, and when the iodide is reduced into thin layers it appears blue. Is it in this manner, or does arsenic enter into a veritable combination with the histological elements? It cannot be doubted that it is a veritable combination, for in the hair, where I have demonstrated the presence of arsenic, there exist no interstices, but simply cones boxed up one within the other; consequently, arsenic must have taken its place among the proper elements of this tissue.

But, in 1865,* I demonstrated that arsenic, taking its place in

* Gubler, "Dictionnaire Encyclopédique des Sciences Médicales;" Article Albuminurie. Paris, 1865.

the tissues, was probably substituted for phosphorus; and I said that in the situations where phosphorus normally predominates, arsenic should predominate when introduced through whatever cause. I applied to the introduction of arsenic into the histological elements the great law promulgated by M. Dumas, the *principle of substitution;* that principle, in virtue of which any simple body belonging to a group takes the place of the substance homologous to it in the same group, in the same way that a metal takes the place of hydrogen in organic compounds.

I said, then, arsenic is substituted, and if it substitutes itself for any other body, it should be found in greater abundance in the tissues which contain phosphorus naturally. This opinion, founded simply on the consideration of chemical facts and laws, has been verified. Within a short period, experiments very well made in this Faculty have demonstrated that, in effect, arsenic takes its place, particularly in the nervous system. But the nervous system is distinguished from all the others by the presence of phosphorus in considerable quantity. You are aware that the chemists have shown it to be present in the entire nervous system, except in the parietes of the cells.

That which Liebreich called *protagon* is, again, a substance containing phosphorus, and he considered it the most essential element of the nervous centres. He was preceded by Gobley and other analysts, who discovered *leceithin*, which is nothing more or less than protagon. All these substances contain phosphorus; and you can see that I was right, and that experiment has demonstrated the correctness of my supposition.

Thus you can very well understand that in searching for the presence of arsenic the nervous centres should be examined as well as the liver, for it is in these centres that it is met with in greatest quantity when there has been slow poisoning, or where poisoning has been produced by massive doses passing through the system during a certain period.

But there is another and more general law. Arsenic does not remain solely in circulation in the blood and in the lymphatic system; it is not deposited alone in the secreting elements, and

does not become substituted for phosphorus solely in the tissue, but wherever phosphates are present.

Wherever there are phosphates there may be arseniates formed. Then, since phosphates exist almost everywhere, since they are found in all the liquids of the economy—for all serous fluids contain phosphate of soda, of magnesia, of calcium, as does the serum of the blood—arseniates may be formed everywhere. Phospho-glyceric acid is, say certain experimenters, in circulation in living organisms in combination with lime.

Thus, phosphorus is everywhere; it is deposited in the tissues, and is in circulation in the blood itself; but there is one system in which phosphorus is still more abundant; it is the osseous tissues, in bone. You know that bone is constituted by the tribasic phosphate of lime, with other phosphates in small proportion.

Arsenic substitutes itself for phosphorus in these combinations, and here is the proof: One day, when I was conversing on this law of substitution, with my learned friend, M. Paul Thénard, he said to me: "I have preceded you; several years since I made the following experiments: I added to the food of certain young animals, which had been weaned, but were developing rapidly, a considerable proportion of tribasic arseniate of lime, in order to see what effect would be produced on their osseous system. I submitted them to this somewhat falsified system of alimentation, and then sacrificed them."

Then, under these conditions, M. Thénard found that in the new layers of bony tissue the tribasic phosphate of lime was replaced by the tribasic arseniate. Can a more striking confirmation be found of this law of substitution, as applied to living organisms? And you may thus understand how arsenic may remain so long in the system, since it enters into the constitution of bone corpuscles, and becomes a part of the organism itself during a very long period.

The destruction or absorption of the elements is assuredly more or less delayed, more or less rapid; but for certain organs, such as, for instance, the hair, particularly in women, the process

is very slowly accomplished. Consequently, you can see how, under these different conditions, arsenic may remain very long in the interior of the economy.

Now, as we have considered the effect of arsenic on the liver and on the globules, what are its effects when it has penetrated into the histological elements? Two cases present themselves for consideration: In the first, arsenic penetrates slowly and in small proportions, and determines simply phenomena due to modification of action in different organs; there is a falling off in the nutrition, comparable to the languid state of the circulation, and we see that the histological elements perform their functions in a less energetic manner.

It seems, when the subjects affected are carefully observed, that there is simply a slowing-up in the functional activity of the various organs, in relation or in keeping with the languidness of the general nutrition of the body. It is thus that we can explain the phenomena observed in arsenic eaters, and how the temperature is reduced in the febrile state, while, at the same time, the condition of the various tissues improve.

But when the tissues are more rapidly invaded, as they are sometimes instantaneously, by massive doses, then the phenomena are different; it is no longer a simple modification in the function (or the performance of the functions) of the various organs or of their nutrition; symptoms of veritable poisoning of the histological elements take place; there is a modification, not only in the rapidity or slowness of their evolution, but there is complete disorder, and the histological elements undergo a veritable arrest in their nutrition and evolution, or, at least, such diminution that there results hindrance in the performance of all the great functions.

And when the quantity of arsenic is very large the histological elements are reduced to a state of impotence; they nourish themselves no longer, and phenomena result similar to those observed when an eschar is produced on the skin.

Then, when you have caused them to perish, what will happen? Phenomena due to consecutive alteration, to necrobiosis, will en-

sue, exactly as if they had perished spontaneously (as for instance a tumor which becomes gangrenous); and in such a case, what will happen for the albuminoid matters contained in these tissues which have perished? A fatty matter will be produced, which is the state of final decomposition of the histological elements, and which is produced also in dead bodies; it is the fat of the cadaver.

Steatosis ensues, then, in the various organs, that is, a fatty transformation, not to be confounded with the formation of fatty tissue. It is a fatty transformation of the parietes of the cells and of the histological elements in general. This steatosis is induced, then, in a certain number of cases of poisoning; but I have already shown you that when the dose of the poison is small the general symptoms observed have not the gravity which we here attribute to them. This visceral steatosis is, then, a phenomenon which may exist or may be wanting, even when the poison has caused death; and there have been cases where death ensued and where no visceral steatosis was found at the autopsy. In certain cases where a moderate degree of steatosis of the liver (for it is this organ that is usually examined, this change being most marked in this gland), has been observed, it is necessary to be very reserved in considering the signification of the post-mortem appearances.

Have all the authors avoided the causes of misapprehension which deceive so many? Have they a perfect knowledge of the normal state of the organ? No: the greater number of those who thus examine organs post-mortem are ready to charge the poison with the production of any little peculiarity which they may find.

This is what happened for Addison's disease; Addison himself described it as an affection characterized by indigestion, feebleness, cachexia, with a bronzed tinge of the skin; and the suprarenal capsules are found, under such conditions, in a morbid state; the first phenomena, those of cachexia, etc., are the effects, the state of these capsules the cause! But since his time the idea has been pushed further, and it has been said that a bronzed coloration of the skin is always accompanied by lesions of these

capsules, and a number of cases confirming this assertion have been put forward. In one such case I objected, "But these capsules that you show me are normal, they are found in just such a state in every individual over twenty years of age, and consequently they have no signification." The distinguished person to whom I made this objection had never thought of examining a normal suprarenal capsule.

There is a published observation in existence in which it is said, "the capsule did not appear much altered, but with the microscope we have found a large proportion of fat." But it is always so, and there is so much fat that with these capsules a milky emulsion may be made.

The cases in which it was thought a pathological condition of the liver existed where the parenchymatous cells were found to contain a considerable proportion of fatty matters, were very often cases in which the liver was in an absolutely normal state.

There has been a work written on the steatosis observed in obese women and in women in the puerperal state; later on, the author was obliged to recognize that this was the normal state; and if animals are killed during the period of digestion, you will always find the liver fatty. Consequently, if you have given them, no matter what poison, it is possible that, in sacrificing them, you will find in the liver the hepatic cells charged with fat.

Consequently, when the liver alone is fatty, too much importance should not be attached to the fact.

The steatosis may be met with not only in arsenical poisoning, but also in almost any case of poisoning; while, on the contrary, it is not always present in cases of arsenical poisoning which have proven mortal, and may be met with in fatal cases produced by other poisons.

The steatosis caused by phosphorus has been long known, and this condition was first observed in that form of poisoning; then arsenical steatosis was described, then that induced by mercury, etc. All these facts are true, but should be received with

the reservation I have made above. More singular still, a high degree of visceral steatosis may be met with in poisoning from substances differing very much from these, as in poisoning by sulphuric acid, or by ammonia.

Electro-negative bodies and electro-positive bodies cause steatosis in an equal degree; and these facts are not isolated; I have seen two cases. I have observed one case of poisoning by sulphuric acid, and one by ammonia, both followed by death, and in which visceral steatosis was found in both cases, as in poisoning by phosphorus. You can then very well see that it is necessary to change the interpretation of this steatosis occurring in the viscera.

I had thought that steatosis, when caused by phosphorus, might result from the fact that under the influence of a state of denutrition, of regressive transformation, insufficient combustion or oxidation ensued in the tissues, and consequently an exaggerated proportion of fat remained in them.

But there is no necessity to call into play so remarkable a causation; it may be said that steatosis is the result of the death of the histologic elements, determined by any poison, whatever may be its nature; when the quantity of the noxious substance is enormous, capable of hindering or suppressing the functions of the organ, and has arrived in the parenchymatous tissues, there are cells which are killed, and these cells undergo regressive transformation, and consequently, fatty degeneration. This is the way this phenomenon should be understood.

Now, we will consider in what situations and in what state arsenic is found in subjects poisoned with it. Several different cases may be distinguished.

If the poison has been recently administered, it must be sought in the digestive organs, and there you will find it in several conditions. As the arsenious acid, which is oftenest employed, is not very soluble, some of it is found in the intestinal fluids. There is another portion adhering to the surface of the villi, to the valvulæ conniventes, or more or less incrusted on the mucous membrane. Then there is a certain proportion which passes, after death, by imbibition, into the tissues of the intestine and

into the neignooring organs. It is a purely physical imbibition. When poison has been administered some time before death, it has first been carried into the ante-hepatic portion of the vascular system; then it arrives in the liver, where it accumulates, for two reasons: in the first place it is carried there directly; in the second, after its diffusion throughout the system, it returns to the liver, because this gland is the eliminating organ for arsenic and the metals.

M. Laborde has published interesting facts concerning poisoning by arsenic; he has observed that, under its influence, the biliary secretion was exaggerated at the moment arsenic entered the liver. Even when it is diffused and has taken its place in the tissues, it is still by the liver that it is partly eliminated.

But when the symptoms have been prolonged, when the quantity of arsenic has been considerable, I said to you that it was necessary also to seek it in the tissues themselves, and not only in those bathed in the blood, not only in the nervous system, but also, and particularly when the poisoning dates far back, in the caducous organs, in the hair. I do not doubt but that it may be found in the nails, which is one way by which the metals are eliminated. Thus I have remarked a brownish tinge of the nails in healthy subjects who take sulphurous baths. This shows that in the nails there is a certain proportion of iron in the normal state. It is for the same reason, when patients in lead poisoning have taken a large number of sulphurous baths, that you will finally notice after a bath that the base of the nail, which is impregnated with the lead, becomes colored.

I said that it was in the interior organs that arsenic should be searched for, particularly in the elements of the nervous system; but the osseous tissues must also be examined, since there we have an entire system where arseniate of lime may take the place of phosphate of lime.

It is, then, in the hair and in the bones, when the subject has been long dead, that arsenic must be sought for, with this condition, however, that large doses have been originally given. Moderate doses, which have been administered during a short

space of time only, may produce the most grave functional disorders, and may even cause death without leaving durable traces; for never, at any moment, has there been a sufficient excess of arsenic that a part might be left to constitute an integral part of the histological elements. The liver and the other emunctories will have had sufficient time to eliminate the poison, so that it will be impossible to find any trace.

This permits us, at present, to understand how death is produced through the influence of arsenic; it is necessary to distinguish between the different forms of poisoning, and if this distinction (with careful discrimination) is not made, you will not properly understand the facts presented to you; you may not only deceive yourself, but deceive also the public authorities who may apply to you. Distinction must be made between three different forms of poisoning.

In one set of cases an enormous quantity of arsenic is given at one time; this poisoning is done by unskillful persons who have just entered on the business, and who give frightful doses to those they wish to rid themselves of. Two things may happen. Either the subject recovers, notwithstanding the largeness of the dose, just as happened for the woman of whom I have spoken, or he succumbs; and if he dies, it may be with simply choleriform symptoms, exactly as if any other caustic had been introduced into the digestive tube; that is to say, there are not only phenomena due to local irritation, but also the reflex and sympathetic phenomena which characterize the choleriform state; the individual may die as if struck by lightning, or he may succumb to the local lesions, or to the reflex phenomena which they induce. But he may also die through all the series of phenomena supervening on the diffusion of the poison throughout the system, and of which I have shown you the exaggeration under the influence of massive doses.

Such, then, is the first form of poisoning by arsenic by massive doses. As relates to the other forms, I will speak to you in the next chapter.

CHAPTER XXIV.

Arsenic (Continued).

Albuminuria, its interpretation. Concerning death by arsenic (continued). Importance of taking into consideration the difference in doses. Modes of poisoning by arsenic.

GENTLEMEN:

Before going further, and before speaking of the two other forms of fatal poisoning by arsenic, I wish to speak to you of a symptom which hitherto has not been well explained; it is the occurrence of albuminuria.

A certain number of cases of albuminuria have been considered due to the passage of the arsenic through the kidneys. But this is a faulty interpretation, which has been applied, also, to poisoning by lead and by mercury, and which provokes criticism in these two cases, just as when applied to arsenic. And the proof that the passage of lead or mercury is not the habitual cause, or worthy of attracting attention, is the fact that in a great number of cases, where the poison is in considerable quantity and has been rapidly ingested, albuminuria is not present.

Albuminuria supervenes in the period of cachexia, and is thus observed ordinarily in chronic lead poisoning. You will see individuals arriving from the white lead factories at Clichy presenting very grave symptoms of lead poisoning, but you will not find a trace of albumen in their urine. But if in the end they fall into a cachectic state, which, in such a case, will be saturnine cachexia, they will have albumen in the urine, and this will continue to be present even when the poison has been completely eliminated from the system. Another proof is this fact, first indicated by Overbeck, in poisoning by mercury. Albu-

minuria, at first present, disappears later, to reappear at a certain period through the influence of a cachectic state.

At a certain period of the affection Overbeck administers iodide of potassium, to rid the system of the poison, which then reappears in the urine, and at this moment albumen is no longer found.

I have observed the same fact in the case of which I have several times spoken. Albuminuria was present, but disappeared the moment that I caused a considerable quantity of arsenic to reënter the circulation. Consequently, the albuminuria observed in cases of poisoning must not be considered as produced entirely by an exaggerated state of irritation at the moment the poison is eliminated from the body in the urinary secretions.

The albuminuria in such cases is but the expression of the general state of the system; the dyscrasia shows itself, as I have often demonstrated, by the presence of albumen in the urine.

We have briefly considered, in the last lecture, the different forms of death after arsenical poisoning, but I have not explained to you the manner of dying when variable doses of arsenic have been employed. This we will now consider.

When the doses are moderate or small, but sufficient, however, to produce certain effects, then the disorders are much more obscure than when massive doses have been taken; the symptoms almost all point to the digestive tube; but the effects produced are none the less dangerous, and death, even, may ensue when the doses have been repeated a sufficient length of time. The first mode of poisoning (by massive doses) corresponds to what I have called poisoning by unskillful, inexperienced hands. This second mode will be observed after poisoning by pretty strong doses, repeated for a period of time.

But the symptoms of this second form may also be observed when pretty large doses of arsenic have been administered therapeutically, and it is necessary that you should be acquainted with the possibility of its occurrence under such conditions.

There is a third form of poisoning, which we must stop an instant to consider. It is that which is executed by skilled

hands, and is produced by small doses. Small doses? It is necessary to understand what is meant by small doses. There are no doses absolutely small, and none absolutely large; for I have shown you that the proper dose varies, according to the general state of the system at the time.

Suppose, for instance, that the dose may be two, three, four or even five centigrams per diem. I say that such a manner of proceeding is of incalculable advantage to the criminal who puts such a plan in execution, and you will easily understand why.

In the first place, with doses comparatively small the symptoms observed are of a less serious nature; you will never observe the terrible effects produced by massive doses. There is no question of choleriform symptoms. You will have simply symptoms of trouble in the digestive organs, nausea, vomiting, loss of appetite, followed by diarrhœa, to sum up: all the phenomena observed in a large number of affections occurring spontaneously or produced by causes differing widely from the ingestion of poison. Such phenomena are observed in dyspepsia and in diarrhœa, or are produced by cold, by heat, by humidity, or through indigestion. Thus you have symptoms much milder than usual, and which, again, have no very evident signification, and therefore do not attract attention sufficiently to cause suspicion. This state continues, and little by little the digestive functions become more difficult of performance; the diarrhœa seems to become constant. But an end is put to all these symptoms; from time to time the medicament is suspended, the thread of life is not severed all of a sudden, and all the dangerous symptoms disappear. There is a sort of amelioration, which lasts for a variable time; nevertheless, little by little the phenomena due to the breaking up of the constitution return; there is a general diminution of strength throughout the system; there is anæmia—everybody speaks of anæmia; it is seen everywhere. Consequently, when a person suffers from troubles in the digestive organs, when there are also nervous troubles, it is thought that all is clear; for nothing is more frequent than to observe nervous symptoms accompanying anæmia.

Again, another series of advantages: the poison is present always in small quantity, and it becomes difficult to demonstrate its presence in any considerable quantity to satisfy the scruples of those who are doubtful of its existence; even when death has been produced and when the poison has not been eliminated, this difficulty would still exist.

But when care has been taken, besides, to suspend from time to time the administration of the poison, when, consequently, there has been time for elimination, the proof of guilt is in part wanting, and does not exist in all parts of the system, as is generally thought; for it is generally imagined that in cases of poisoning the substance which causes death can be found in all parts of the organism. Under the conditions I have specified, it is not so; not only the poison has been in part eliminated, but the little that remains is not diffused throughout the system; sometimes it has not gone further than the liver. It remains fixed in this organ, and on examination no noxious principle is found in the elements of the tissues where it is habitually deposited. Consequently, after an official autopsy has been made, its presence cannot be demonstrated, either in the bones, or in the brain, or in the hair.

With even more reason, then, under such conditions, no grave symptoms are observed; nor any functional disorders which would be without organic lesions if they were present; there is no paralysis before the patient succumbs, and when he does succumb, no steatosis is found. Steatosis may be wanting when the doses have been excessive, but it is never found except when they have been so.

You see what obstacles are accumulated in the path of experts in medical jurisprudence, and how difficult it is for them to demonstrate that poisoning has taken place. They cannot bring forward any very significant fact, they cannot demonstrate the presence of arsenic in the brain, they cannot produce any considerable quantity of the poison; the entire demonstration is evidently incomplete.

Notwithstanding all these difficulties, you will soon see that

it is possible to arrive at a demonstration of the presence of poison.

But, first, we should consider whether it is really true that two or three centigrams of arsenic per diem may in the end produce death? There are, as I have told you, individuals who eat arsenic, and others who, without having thus acquired comparative immunity, resist it for a period.

Arsenic should not be considered merely a corrosive poison, acting only by the grave lesions it produces, exciting more or less active inflammation, with eschars and all the lesions that ensue, as when a piece of caustic potash or a considerable dose of chromic acid falls into the stomach. It is not thus that it acts; or, at least, if it acts thus, it has also other effects, resembling those produced by emeto-cathartics.

Arsenic exercises a poisonous influence on the digestive tube, even when no appreciable irritation has been caused; it induces nausea, just like tartar emetic, like sulphate of zinc, and like sulphate of copper, that is to say, in virtue of a property, special to it, if you wish, but which belongs also to a group of bodies, it determines an effect on the peripheric end of the pneumogastric, which is shown by the existence of nausea.

Can emetin and substances of analogous action be considered escharotic? No; they are substances which have a peculiar action on the form of sensibility found in the stomach and digestive tube. This will make us understand why it is not necessary to introduce large doses of arsenic to produce its nauseating effects, no more necessary than to introduce large doses of sulphate of copper. Twenty centigrams and often even seventy centigrams will be sufficient.

It may be mentioned, in passing, that there is another error which is becoming prevalent, that is, that the salts of copper are incapable of causing poisoning. I do not pretend to say that the noxious effects of these salts have not been exaggerated, that they have not been considered more poisonous than they really are; but to say that they are absolutely free from poisonous properties, is to place one's self in flagrant contradiction with the facts

observed, and ignore what is at present known concerning the drug.

If copper is introduced in very small doses, so as not to produce any effect on the digestive organs, it may thus enter into the general circulation and be eliminated continually as it is introduced, without provoking any grave symptoms. But if the dose is sufficiently large to provoke nausea and vomiting, with all the phenomena observed in such a case, and if these symptoms reappear each day, then you may see the subjects fall into the cachectic state observed when smaller doses of arsenic—for this poison possesses greater energy—have been administered. But, in reality, the mechanism by which the lesions are produced and the co-existent phenomena, are similar.

I will now attempt to show you in what manner arsenic in single doses, producing this nauseating emeto-cathartic action, may nevertheless, when administered in repeated doses, determine the injurious effects with which you are already acquainted, which have been indicated in judicial cases, and which may even cause death.

A substance capable of inducing emeto-catharsis produces an exaggerated gastro-intestinal secretion, which is not simply mucus, but contains also so large a quantity of albuminous serosity that if treated by heat or the acids it coagulates.

There is, then, spoliation of the system; it is as if a serous bleeding was repeated at short intervals.

When vomiting is produced it is an action which requires considerable effort of all the powers of expiration, and consequently there results a loss of strength. As proof of this it is sufficient to notice the state of prostration into which an individual who has just vomited is thrown.

Consequently, as we have seen, there is a loss of strength through vomiting; and even oftener, through emeto-catharsis, are observed those phenomena, due to the reflex sympathy excited in the general system, which accompany abdominal diseases and are *en rapport* with the obstacle existing to the performance of the functions of the sympathetic nerve.

These phenomena merit the name of *peritonism*, or of choleriform affections, which I have given them. You are all acquainted with the form of cholera produced by tartar emetic, which may be induced by five centigrams of the drug, and which, when death ensues, may leave but a slight redness, without any veritable inflammation determined by the noxious substance.

What really happens when this choleriform state is observed? There is extreme prostration; great disorder in the performance of the various functions; hæmatosis is hindered, the circulation languid; the pulse is small and becomes very slow or excessively rapid. If the combustion is suppressed or becomes less active, what happens? The rehabilitation of the tissues becomes impossible; there is no reparation of the losses undergone by the organism, and consequently there are languidness and impossibility of general nutrition, caused by the suppression of the gastric functions, or at least by the diminution in the functional activity of the stomach. Consequently, as you see, many obstacles are placed in the way of the performance of the various functions, and in the way of general nutrition of the system. And if these obstacles continue to exist, if, instead of lasting for days, they are present for weeks, you can understand what will ensue: losses which cannot be repaired; insufficient nutrition; consequently, little by little, organic decadence, marasmus, and death.

I do not pretend that the small doses of which I have spoken suffice to kill everybody; I am of opinion that many among you would survive such doses, because you are possessed of that vital resistance which will enable you to surmount many obstacles in life.

But suppose a puny creature, with a shattered constitution; suppose that this being has already suffered from lesions more or less serious in the digestive organs; you will see produced from small doses grave symptoms which may have the fatal character with which I have just endowed them.

This is so true, that when you employ arsenic in therapeutical

doses, it will happen to you to meet with cases in which the digestive organs are of extreme sensibility, and where arsenic will cause symptoms more or less serious.

This is remarked frequently by practitioners who employ arsenic against intermittent fever; they administer two or three centigrams from the beginning, Boudin even giving five centigrams; and it happens that in a certain number of cases these doses cause vomiting, diarrhœa, and symptoms of collapse, due to the sympathetic effects which characterize any lesion or affection of the sympathetic nerve. You find yourself then obliged to cease the treatment by this drug.

When you meet with such individuals, it is clear that if you persist in the use of the drug, you may in the end determine grave symptoms. And when these symptoms, which, if they lasted but one day, would not be a source of great danger, are continued for a considerable time, there ensues in the end that diminution of strength, that alteration of nutrition, in one word, that state of cachexia, which may very readily terminate by causing death. It will suffice to breathe, if it may be so expressed, on this shattered organism, to bring about irremediable injury.

Here a question presents itself for consideration which might have been taken up when speaking of the occurrence which gave occasion to this discussion. It is to know of what nature may be this last breath, or act, which may extinguish an existence so deeply shattered. It may be almost anything; perhaps a last dose of the poison, or a trifling intercurrent malady. The patient is already very much shattered; he takes cold, suffers from fever. he sinks, and the little that remains of life is extinguished.

There is another circumstance meriting attention; it is the possibility that the poisoning has been repeated several times. I have heard a magistrate say that criminals themselves generally point out the way to follow in order to discover the particulars of the crime; no matter how well prepared to keep silent, they allow to leak out, in the end, something concerning the subject which fills their thoughts, as robbers, according to what

detectives say, always turn at street corners, to assure themselves that they are not pursued.

In a recent trial, the accused said, "I do not know but that, by chance, belladonna may have been taken." It is to be regretted that this clue was not followed up. It is certain that sometimes even a quite medium dose of a vegetable poison, always difficult to detect, suffices to destroy life. It is the more difficult to recognize its presence since it will come in contact, in the digestive tube, with elements of destruction, acids, alkalies, substances in a state of fermentation, the ferments normally present, as pepsin, diastase, pancreatin, and ferments accidentally present, which exist everywhere, by virtue of the law of panspermism, with which you are all acquainted.

Consequently, you see how easy it is to understand how death may occur even in cases where the symptoms of poisoning have remitted, from time to time, in intensity, and where the doses have been moderate. It suffices that the system of the individual, in these cases of intermittent poisoning, be predisposed; that there be great susceptibility of the digestive organs, with great constitutional feebleness. Great attention must, then, always be paid to the state of the system of the individual who has been poisoned.

We can, then, at present, understand the extreme diversity in different cases, the resistance presented by one subject or the fragility of another. Some resist the most violent, the largest, most massive doses—this woman, of whom I have spoken, recovered after taking eight drachms, at least, of arsenious acid—while others succumb under the least pretext, if I may use the expression; so that the minimum fatal dose may be twelve, even ten centigrams; and, on the other side, the maximum tolerated may reach as high as eight or ten grams; thus differing in the proportion of one to ninety, or even one hundred.

What is the explanation of this difference? It is found in the constitutional state of the different individuals, as I am about to indicate to you. There is extreme diversity as regards the susceptibility to impressions of the digestive organs; as regards

the receptivity of the entire system for the poison, and as regards the facility of elimination.

If you suppose an extreme tolerance for arsenic on the part of the stomach and intestines, you will not witness the production of any of those local disorders which you have just seen to produce death. You will not observe any symptoms in the mucous membrane of the intestines, nor any appearance of sympathetic or reflex phenomena. If, at the same time, the activity of nutrition and absorption in the tissues is very marked, the poison will not be deposited.

When a subject is young his tissues are rapidly renewed; nothing remains long unchanged in him. Under such conditions there will be less accumulation in the parenchyma of the different organs and in the tissues of the nervous system than under contrary conditions. You are, then, yourselves, under favorable conditions. But when with this the kidneys are largely open, when the urinary secretion is abundant, and consequently the arsenic ingested can freely pass out of the system by this open way, it is clear that this individual, whose digestive organs tolerate so well the irritation produced by the poison, in whom nutrition is so well accomplished and the bile so freely formed and secreted, can ingest moderate and even strong doses without the production of perceptible symptoms. This subject will be one of those who resist even massive doses of arsenious acid. I do not say that such resistance is not an exceptional fact; but it happens.

Suppose contrary conditions—digestive organs exceedingly susceptible to impressions, which nevertheless, through feebleness of the various functions, cannot disembarrass themselves of the poison which injures them; nausea, prostration, exhaustion, collapse will be observed. Again, the general condition of the system is bad; advanced age, constitutional state, all will tell; organic renewal is slowly brought about; the "nutritive whirlwind" of Descartes has become slower. Suppose that in this same subject the secretions are not at all abundant, the skin does not well perform its functions, the liver secretes little, the urine

is scanty. Under these conditions doses relatively small will remain, will be delayed, finally will accumulate in the tissues, and in the end will determine not only local but also general symptoms; not alone a species of intermittent poisoning, but generalized arsenicism through diffusion of the poison. In many cases, under such conditions, all that will be observed are the symptoms induced by the local effect of the poison and through sympathy, and which are symptoms always accompanying arsenical poisoning.

Your opinions on this subject should, then, be fixed, as it seems to me. I have exaggerated nothing; I have shown you, in good faith, the effects produced by arsenic, as I understand them, and as I have observed them in a large number of cases.

Now we can approach the consideration of a question which, though of a somewhat different nature, is none the less interesting from a medico-legal point of view. It is not sufficient to know that the facts are as above presented; it is also necessary to know how to recognize a case of arsenical poisoning.

I will commence by a declaration which should head all discussions on diagnosis; that is, that there does not exist any one fixed pathognomonic symptom which must necessarily be present.

The existence of pathognomonic symptoms has long been believed; the lenticular, rose-colored spots were considered an evident sign of typhoid fever, and opinions on their nature have varied with the denominations of the disease; to-day we know that these spots may be wanting in typhoid fever and may exist in other affections, and particularly in acute miliary tuberculosis. These signs have long been believed in, the more so because specific causes and something special about disease in general were believed in.

A return was unwittingly made to the doctrines of the middle ages when cancer was considered to be a parasite which devoured the tissues; and so much faith was put in this interpretation that fresh meat was used to turn aside its action from the tissues.

It is the same thing when it has been asserted that there exist

characteristic cells in each species of tumors. Always the same error, sometimes gross and apparent, again hidden under scientific expressions. I will add that there is no absolutely necessary symptom in the history of any disease. This declaration made, it remains but to say, to complete it, that the diagnosis of a malady is made, not by one or two symptoms, but by the ensemble of symptoms. It is not only necessary to have all the symptoms present, but the malady must develop itself in the usual way, the symptoms occurring in determined order. So much so that you may in different maladies have the same set of symptoms, but occurring in a different order.

For instance, typhoid fever, has the following evolution: headache, fever, the patient takes to the bed, diarrhœa follows and remains the predominant symptom. Take cholera, on the other hand, and the choleriform affections; in these you remark the same symptoms, if you take them one by one: very intense fever, grave intestinal lesions, headache. What is the difference? The symptoms are the same, but their evolution is different. If the patient syas that in the commencement he had great aqueous diarrhœa, that this diarrhœa has little by little become less marked, that the fever, at first imperceptible, has become intense and reduced the subject to the state in which you find him, then you will consider that it is a case of choleriform diarrhœa with consecutive fever, induced by reaction. The other patient, in whom the début of the affection was slow and without prominent symptom, the diarrhœa gradually increasing, will cause you to think of typhoid fever. Apply this mode of reasoning to arsenic poisoning as to every other affection.

It is by the peculiar course of the affection, notwithstanding the absence of a certain number of grave symptoms, that you will in the greater number of cases recognize its nature. Exactly as if you detach a stone from one of the towers of Notre-Dame, even from one of the angles, there would be no difficulty on that account in recognizing the tower. Even if several stones were removed there would be no difficulty in recognizing it.

It is just the same with a symptomatic series; if a part is wanting you will still be able to recognize the malady. The most special phenomena of the disease may disappear, one by one, or even by groups, without hindering its recognition. For instance, in arsenical poisoning the burning sensation in the throat may be absent. It suffices, to prevent its appearance, that the poison be given in pill instead of in a liquid form; and nevertheless, this symptom seemed so characteristic that in the late case it was considered necessary to have demonstrated that the patient suffered from burning in the throat and from thirst; that is, to show the existence of a contingent symptom, arising from the topical action of the poison at the entrance of the respiratory organs.

CHAPTER XXV.

Arsenic (Continued).

Diagnosis of poisoning; difficulties encountered; no pathognomonic symptoms; medico-legal considerations. Imbibition by certain substances; histologic deposits.

GENTLEMEN:

I demonstrated to you, in the last chapter, taking arsenic as an example, how little dependence could be placed on one or two symptoms, even though reputed characteristic; and I said to you, in concluding, that the much talked of burning in the throat, on which legal authorities have so much insisted, may be wanting and is wanting in all cases where the poison has been directly introduced into the stomach, without having come in contact with the throat.

It is the same for cutaneous eruptions; in this case they wished to find them, as if such eruptions were not wanting in the great proportion of cases, their presence being due to topical action, to the effects produced by arsenic in fine dust impregnating the skin. On the contrary, the proper arsenical lesions are due to the passage of the poison by the cutaneous emunctories, and are wanting in a great number of cases. You see, then, what dependence can be placed on the occurrence of this symptom.

Consider the nervous symptoms; in almost every case of arsenical poisoning these are observed, yet paralysis is of so exceptional occurrence that certain authors even deny its existence. The existence of arsenical paralysis cannot be doubted; but it is not of common occurrence; consequently, you have not the right to demand its presence in order to fully prove that poisoning by arsenic has taken place.

I may say the same of steatosis; it is characteristic of poisoning by very large doses, and it may not be produced even with such doses, since in the case I have so often mentioned recovery took place; and certainly the existence of fatty degeneration of the different organs is incompatible with the continuation of life.

Consequently, as you see, here are quite a number of symptoms reputed characteristic, and which not only may be wanting, but which, to a certain extent, should be wanting in many cases. On the contrary, these same symptoms may be met with in other affections; this burning sensation in the throat—all the acrid poisons determine it; poisoning by ammonia is accompanied by a horrible sensation of burning heat, of veritable scalding in the throat, and excites unextinguishable thirst, more peremptory than if the subject had been poisoned by arsenic.

The vomiting and gastro-intestinal symptoms capable of taking a choleriform aspect are observed as well after poisoning by metallic substances, such as sulphate of copper, or of zinc, as after arsenic has been taken.

This series of grave symptoms, due to the impression made on the abdominal portion of the sympathetic nerve, are observed in all cases of poisoning, even by moderate doses, or during a time when choleriform diarrhœa is prevalent; they have been observed when only five centigrams of tartar emetic had been taken.

The paralysis, when it exists, is certainly of a peculiar type; but would you be willing to conclude from this that you have before you a case of arsenical poisoning, when you have also an identical form of paralysis in lead poisoning and in that produced by mercury?

I have shown you an example where the great authority of Duchenne corroborated what I have said; it is a symptom which may be observed after poisoning by any substance, but particularly in poisoning produced by lead, ammonia, and sulphuric acid. Consequently, you can see that paralysis is a symptom of slight value as regards the diagnosis of the case.

Will you then conclude that the diagnosis is impossible? That because certain significant phenomena are wanting, because certain symptoms may be observed in any case of poisoning, that all means of diagnosis are wanting? No; diagnosis is not impossible; but it is necessary to have present a certain ensemble of symptoms, undergoing evolution in a certain determined order, and the conditions under which they are observed must be taken into consideration.

What is observed in the great majority of cases are the gastro-intestinal phenomena, common to most cases of poisoning, but which acquire value through the conditions under which they may be observed; vomiting, or at least nausea, may be present; atonic dyspepsia with catarrh, or true diarrhœa, prostration of strength, and then certain co-existent phenomena; slight frigidity, a more or less notable diminution in the force of the cardiac pulsations, in a word, all the adynamic symptoms which accompany diseases of the digestive organs. I repeat it, these symptoms are observed in cases of poisoning by different substances. But when the symptoms persist, or intermit from time to time, always under the same conditions, and if there is an interval of complete rest under such conditions, and in the absence of the ordinary causes which give rise to such phenomena, you will find yourself under the obligation of considering if there may not be some outside artificial cause intervening to produce the symptoms observed. When you observe these symptoms supervene, you are obliged to take into consideration the very grave hypothesis of poisoning. This is what happens in a certain number of cases, and notably in the recent affair which has caused this digression.

This supposition will acquire still more importance when death ensues, and the physicians, who, during life, had not been able to determine any cause capable of producing the symptoms observed, cannot, even at the autopsy, find any of the lesions which habitually determine gastro-intestinal disorders. During life it may have been thought that an ulcus rotundum existed, that a true inflammation, or tuberculous lesions, or advanced anatomical changes in some organ, would give the explanation of the serious

symptoms. But no; the autopsy shows no anatomical lesion. When this is the case, what before was but supposition becomes a probability.

If it be added that the organs which necessarily would come in contact with the arsenic, and come under the influence of its antiseptic properties, are in a state of perfect preservation, as if death had just before taken place; if the stomach preserves its greyish-rose tint, if the intestine has its normal coloration; if all this is the case, then the presumption that poisoning has occurred becomes of extreme probability.

But the observations of the physicians alone will be insufficient. The chemist makes his examination and reports; yes; in these organs, which have seemed to enjoy almost entire immunity from putrefaction, notwithstanding the period of time since death took place, in these organs I find arsenic, in very notable proportion, and I present you with capsules covered with spots.

Do you not find that under such conditions the presumption of poisoning may be considered as proven?

And if in conjunction with this, none of the grave lesions possible of production in the organs observed can have intervened to induce the symptoms observed during life; if the topographical distribution of the arsenic is taken into account, it being found in the intestine and in small proportion in the liver, but not in the other organs, the presumption of poisoning becomes almost a certitude.

But when the life of a human being is in the scale, almost a certitude is not sufficient; absolute certainty of the fact is required.

And in that the duty of the expert differs widely from that of a member of the jury; the latter has the right to have his private impressions regarding the case, to judge it somewhat through intuition; he allows himself to be guided by the moral and physical aspects of the facts.

The expert has no right to intuitive opinions, and can allow himself to be guided solely by the facts from which he draws conclusions. A private opinion should never take the place,

for him, of scientific conviction. On this account I said, in a recent trial, poisoning has, in all probability, taken place. But if I had been a member of the jury I should have voted yes. At present we may pass in review the different objections made against this interpretation of the facts in that case.

The two experts, both men of probity, both convinced, agreed in saying: "There is a certain proportion of arsenic present (this was difficult to deny, for arsenical spots on porcelain were shown), but it is not in sufficient quantity."

How? There is not enough! But there is always too much! Should any be present in the normal state? I very well know that Raspail, who in a certain trial sought to terrify the judges, said: "But, Monsieur le President, I consider it possible for me to demonstrate the presence of arsenic even in your armchair." Such an assertion does not even merit serious attention.

Without doubt arsenic is present in many substances—in candies, in artificial flowers, which are much less worn than formerly, but it is not so widely disseminated as has been pretended. The much talked of curtains containing arsenic were cited, but the lining did not contain any, consequently they could not have caused the poisoning of the patient. But arsenic was found where it should not have existed. A short time ago I was speaking with M. Thénard, who, as a chemist, had followed the trial. He said to me: "Your reserve was much to be praised; but to me the culpability of the accused was evident; even if there had been nothing but the facts brought forward by the experts and not contested, except as to their interpretation, there was sufficient proof."

Yes, it is evident that sufficient proof existed, for if we go back to historical cases where poisoning certainly occurred, and in which the proportion of arsenic present was determined, we see that in a certain number of cases there was no more, and sometimes even less, than has been shown to exist in this case.

Thus, in the Lefarge case there was no more than a milligram, or even half a milligram, found and extracted, while in this case

M. Lhôte considered it possible to find, in the whole digestive tube, four milligrams.

You can then see that even considering the history of arsenical poisoning, the quantity found was sufficient to demonstrate the reality of the poisoning. Another argument brought forward was that no arsenic was searched for in the brain. I have, in advance, put you on your guard against exaggeration of the value of this argument. I have shown you that in poisoning by small or minimum doses, which, during a certain time are no longer given, the poison enters but a certain part of the organism; it arrives in the liver, in the large gland which arrests mineral substances, and if it passes into the circulation the proportion is small, and elimination taking place, but an infinitesimal part remains in the substance of the different organs, and in the tissues of the nervous system in particular.

Consequently, there was no necessity, in this case, to demonstrate the presence of arsenic in the brain. Other arguments were made, and I wish to pass them in review, because at the moment they were presented I felt an intense desire—which I resisted, and I think properly—to take up these arguments one by one, and—I don't fear to say it—demonstrate their complete fallacy.

I did not do so, and for the following reason: I had formed a personal opinion, and I determined to maintain it, to the effect that poisoning had in all probability taken place. And if I had entered into a discussion I might have allowed it to be seen that, in my private opinion, it was certain. This I did not wish, for I was an expert and not advocate. Here are the series of arguments invoked: First, it was said, and it was the feeblest argument, "There is a charge of arsenical poisoning. This is astonishing! I am acquainted with two forms of arsenical poisoning, which have been well described, and try as I may, I cannot reconcile the picture presented of this case with either of the forms with which I am acquainted."

It is just as if one said: Typhoid fever? But there are only two forms, ataxic and adynamic. The reply is: in a disease of this kind there are as many forms as there are patients; it is

by mental effort and study that these two forms have been separated from the others; but besides them do we not find other forms? Do these two forms include the slow, nervous form, etc.? In the same order of argument is the absence of the peculiar Hippocratic countenance, with sunken eyes. This appearance is noted only in certain forms, and as well when tartar emetic has been used as with arsenic, and occurs when the dose is large and the lesions of intense gravity; otherwise it does not exist. But I will not insist on such an argument.

But, again, here is a series of arguments which appeared to make considerable impression—I will not say on the jury, who did not appear to understand their value—but on the public at large. First, it was said certain omissions occurred in the examination; thus, the presence of arsenic was not searched for in the brain. I have already shown what should be thought of this circumstance. But, again, the meningeal membranes were not examined to determine if tuberculous granulations existed, and if granulations were there present all would be explained.

Is it possible, I would ask, that a physician be so unacquainted with the course of disease as to confound the symptoms of tuberculous meningitis with gastro-intestinal disorder, characterized by vomiting and diarrhœa, with absolute integrity of the intellectual functions, and the absence of any symptom of lesion of the nervous centres? Can it be admitted that such lesion would have explained all? It was said, also, that if steatosis of the kidneys was found all would have been explained; that the lesion of the kidney might have been accompanied by uræmia, which would have accounted for all the symptoms.

I am not acquainted with any form of uræmia—and I have devoted much attention to albuminuria—which presents this absolute intermittence in the symptoms. I do not know any form which has an exclusively gastro-intestinal character, without ever presenting symptoms pointing to the nervous centres. I am unacquainted with any form of uræmia existing independently of the other classic phenomena of albuminuria, such as œdema, etc. Consequently, I do not believe that uræmia, in

any case, could explain the phenomena which were observed in this case of poisoning.

It was a matter of regret, also, that the large intestine had not been examined, because, said the author of this remark, the woman had suffered from typhoid fever, and we know that in typhoid fever the lesions are found in the large intestine. If a hospital externe had said the same thing at a competitive examination he would justly be rejected, as in typhoid fever it is the small intestine that is affected, and not the large. But the large intestine could be brought into argument, as only the small intestine had been opened. No importance need, then, be attached to this argument.

Then the condition called pernicious anæmia was brought into play. Ah! pernicious anæmia. Most of you know what that means, although the affection is of recent creation. It is that state of profound, progressive anæmia which often, in effect, terminates by death, and which the physician cannot understand. It might be called perfidious, rather than pernicious. It places the physician in an uncomfortable position. Better informed practitioners generally perceive, or at least, suspect the cause, and the number of cases where this cause has been determined and proven is sufficiently considerable to demonstrate that very few cases of pernicious anæmia are ever met with, but that such cases are, in reality, the symptomatic expression, the apparent manifestation of some general morbid condition of the system, which may be ranged under one of the diatheses with which you are acquainted. Cancer exists in some cases; again, and oftener, the patients are tuberculous or consumptive. These are the two great constitutional maladies which oftenest induce pernicious anæmia. And this is so true that I have been able to make the diagnosis without any very marked local signs of a tuberculous affection, simply from this progression, this fatality, in the course of a case of anæmia. I have called it a state of anæmia attending consumption. Since then, taking into consideration this view of the subject, a correct diagnosis has been made in a number of cases.

My young friend, Dr. Lépine, of Lyons, has met with cases which seem to confirm this view of the subject. Consequently, if this view is correct, the great number of cases of pernicious anæmia leave traces behind them. It is possible that while the patient lives no determination of the cause of the disease can be arrived at, but when the autopsy is made tumors are met with. Or, as in this case, nothing is found either in the intestines or elsewhere. Some cases were cited in which death occurred with symptoms of anæmia, and in which absolutely nothing was discovered at the autopsy, and a case relating to an illustrious personage was brought forward. We will not speak concerning the real facts of this case; we will consider it simply as related in the account by Alphonse Daudet. In it you will find the history of the symptoms observed recounted with as much fidelity as he could bring to bear on the subject.

As we are contemporary, as these facts are of recent occurrence, we know that if no considerable lesions were found, perhaps the cause of death might have been excess in the use of mercurial preparations. This supposition corresponds with rumor, and there was good reason for suspecting it.

And this was the fact brought forward! When circumstances are so doubtful should such a case be brought forward as a scientific fact? To sum up: you can see that the objections made have no great weight, are not of great force, and do not stand before a scientific examination of any precision.

To resume the facts in the case we have been considering: It is impossible to establish absolutely and rigorously the demonstration of poisoning. But if we unite this ensemble of facts on one side, all the symptoms which accompany the introduction of somewhat large doses (say, for instance, five centigrams) of arsenious acid per diem, symptoms with which we are well acquainted from having observed them in the treatment of intermittent fever; if we consider the presence of such symptoms, their constant repetition under similar circumstances; if we add to this, that no organic lesions capable of producing death have been found; if at the same time it be found that the digestive

organs are not putrefied; if, finally, it is said that a sufficiently considerable quantity of arsenic has been found to enable a very skillful chemist to affirm that four milligrams could be collected, surely there is enough to establish a quasi-conviction of guilt.

I say quasi-conviction, for when the gravity of the affair is taken into consideration, it is proper that no possibility of doubt exist; and all the hypotheses imaginable must be passed in review before declaring that only one, which is the bad one, is proven. In fact, I believe that judgment in this case was well rendered and in accordance with the facts, and such was the conviction of all who had not allowed themselves to be carried away by illusions.

Now that I have spoken to you at length concerning arsenic, I will return to the general question, which has, it might be said, been interrupted by the consideration of this case.

I wished to show you how arsenic penetrates; how it is distributed, how it arrives in the interstices of the various tissues. After having shown you, by this example, the particulars relative to the great and difficult question of the rôle or action, and particularly in relation to the introduction of remedial or toxic substances into the system, I will return to the general question, by making application of the facts which you have just learned.

What, then, is the course of substances introduced into the economy? I have shown them to you absorbed and in circulation in the ante-hepatic vessels, delayed in the liver, then overflowing and carried on in the general circulation, hidden or not by the plasma, and, according to the quantity introduced, having greater power for the production of toxic phenomena by affecting the globules and hindering hæmatosis; finally, through the parietes of the vessels in a free state, or incorporated in the plasma, and finishing by becoming incorporated in the parenchyma of the tissues themselves.

Well, when these substances penetrate into the tissues, they may be under various conditions: Sometimes they are simply introduced, like water, by interposition; again, on the contrary,

they are mixed with the plasma, then they go to take place in the tissues, or in the substances called proximate principles, such as those which I have mentioned. It is thus that it happens that arsenic and other substances follow the same general rules, particularly mineral substances.

But in such case, what is the mode of distribution? Why does one substance deposit in one place or organ, another in a different situation? In virtue, as I have already said, of chemical affinity, substances substitute themselves one for the other. Thus, phosphorus may be substituted for arsenic, as, also, antimony, which very much resembles arsenic, though it be a metal.

Chlorine is normally present in the economy, and bromine and iodine may, in part, replace it; substitution occurs in the different compounds, and in the different tissues which contain these same compounds. Selenium may be substituted for sulphur, and, again, oxygen and sulphur may be substituted one for the other. Calcium, another substance normally present in many tissues, as you are aware, may be replaced by strontium, by barium, and by lead; and for the same reason that I predicted in advance that arsenic would be found in the nervous system, I am convinced that barium and lead would be found in situations where calcium is present. Iron is normally present in the economy. Manganese may, in a certain number of cases, be substituted for it, so that if chlorotic patients are not benefited by chalybeates, their systems may be improved by introducing considerable proportions of manganese. Consequently, here is another proof of these chemical and physiological substitutions. Zinc might, even, be considered as taking the place of these two metals. This is, then, what happens for the metals; I am convinced that something analogous happens for organic compounds, for those species of radical substances which may be substituted one for the other in the chemistry of the living organism.

I will now speak to you of certain facts which do not find any parallel in the history of arsenic. You have seen arsenic taking its place in the tissues, but you have not seen it produce effects analogous to those induced by certain substances which act

simply as bodies infiltrating the histologic elements, or as bodies which are simply dissolved in certain other substances normally present. Thus, for instance, alcohol, ether and chloroform possess, as you know, the property of dissolving fatty bodies. When poisoning by these substances has taken place, they are found in large proportion in the brain, exactly as if they had come in contact with a substance with which they have a species of affinity. This fact is repeated for the alkaloids. The singular analogy existing between the alkaloids, proteic substances and fatty matters has been demonstrated.

It seems as if the alkaloids were intermediary between fatty and proteic substances. They also deposit themselves in the histologic elements of the nervous system, and it is on this account that they induce so marked effects during the period they are there present.

These three modes: imbibition, a sort of amalgamation and penetration of analogous molecules, which act by dissolving one another and finally undergoing chemical integration with organic tissues; such are the three different modes by which active substances penetrate into the economy. But there is another manner, very interesting, which has long been known, but the interpretation of which is difficult. I have shown you that substances which during a certain period are in the state of principles foreign to the economy, may become united with some of the tissues, but are mobile, and after a time are evacuated.

But in other cases where mineral substances have been introduced a portion is irremediably immobilized; it remains in one place, and while all about it changes, it remains in the same state. For instance: when silver is administered—the nitrate of silver given to paralytic and ataxic patients, to subjects in tabes dorsalis—when the drug has been taken for a sufficient length of time, at first a simply grayish coloration is observed, which soon becomes darker, and finally the skin may acquire an olive tint. It is difficult to understand why, when this coloration is produced, it should in the end become dark and indelible.

As I have already said, and I repeat, there is but one phenomenon

which will occur with certainty when silver is administered under these conditions; that is, this disagreeable coloration of the skin. When the matter inducing this tinge is examined, it is seen that it is composed of silver under a form not easily determined; to some observers it is an albuminate; to others, a chloride; others, again, consider it silver reduced to the state of an oxide.

But the fact is, once deposited in or thus mixed with the deeper elements of the superficial layer of the skin, the metallic substance remains fixed. And this, which is true for silver at the periphery, happens also for internal surfaces. It causes staining of the gums, just as does lead. When caused by lead a different coloration is observed in the gastro-intestinal mucous membrane. These deposits are very strange, for how does it happen that while the pigment cells themselves disappear, these spots produced by mineral substances do not disappear? It is difficult to determine why, but the fact is certain. You see, then, that certain metallic deposits are produced after the internal administration of substances which are capable of forming compounds or insoluble substances.

I wish in the next place to speak of the manner of elimination of the various substances thus introduced into the organs. There are substances, as I have said, almost in the free state, simply dissolved in the plasma; and others which form an integral part of certain organs. Those which are free are taken up with great facility by the circulation, and appear very soon in the excretions; those, on the contrary, which are attached to any organ, can enter but tardily into the circulation. It is thus with substances which may become substituted for principles normally present; you will see such substances long delayed. I have given you the limits for arsenic. You will find that they are longer for other substances. This elimination is accomplished in two ways: Sometimes they are introduced into organs which I call caducous—the nails, the hair, the epithelial surfaces—and they are thrown off with them.

It is the same phenomenon seen in plants; th leaves serve them as means of elimination for mineral substances Thus the mineral substances entering a tree are in great quantity;

nevertheless they are not found afterwards in the wood, because they are deposited in the leaves, which, like hair, are caducous (or destined to fall). When, on the contrary, the substances are fixed in elements belonging to permanent organs, then they remain just as long as the histological elements, of which they form a part, themselves last.

Unfortunately, we are unacquainted with the length of time that histological elements last. We know that the blood globules last but a few days, but it is probable that other histologic elements last longer; consequently we cannot determine, in advance, how long mineral substances accidentally forming part of them may sojourn in the system. I have said that there are substances which remain longer than arsenic. It is necessary to say, generally, that these are mineral substances, precisely because they take a permanent place in the tissues, and particularly, because they act as alteratives, agents which I designate as *metatrophic.*

Let us consider, as examples of substances of rapid elimination, the alkaloids. These are organic matters which take no part in the formation of tissues, and which are speedily eliminated in a few hours, or, at the latest, in a few days. The different salts, bromides, iodides, or the neutral salts, are eliminated also with great rapidity. But the mineral substances are, I repeat, long delayed. Thus iron, which enters the globules, manganese, mercury, antimony, arsenic, copper.

I have said that arsenic might not disappear for thirty, thirty-five, or even forty-five days; Orfila said fifteen days; but I have shown you that after forty-five days there was still arsenic present. Antimony remains three months in the economy; copper and mercury six, seven, or eight months.

During the period of their sojourn these substances produce their alterative effects. Consequently, such medicaments can be considered as producing effects for a long period of time.

It is difficult to demonstrate what becomes of sulphur, or phosphorus, when excessive doses are employed; but it is possible that they enter and become an integral part of various organs, act like metals, and sojourn there for a long period.

It has been remarked by physicians, at mineral springs, that the effects of these waters have a duration of several months, and it is not necessary to recommence the treatment until such a period has elapsed, as is required either for sulphurous waters or for phosphorus, when a purely medical treatment by them is undertaken.

CHAPTER XXVI.

Elimination of Medicaments.

Variable sojourn of different substances in the organism; causes of this variability; variable rapidity of elimination.
Choice of elimination made by medicaments.

It is not easy to understand why different substances remain so long in the economy. There are, however, certain circumstances which might be mentioned to explain this sojourn.

In the first place it is evident that the more thoroughly the substances penetrate into the organism, the longer will be their sojourn. If it is a volatile substance, acting on the globules, it is clear that the incessant exchange of gases going on in the interior of the organism will cause the speedy separation of these substances and their consequent disappearance from the economy. This is what generally happens, even for the oxide of carbon, unless it kills the subject. When it is present in feeble proportion, after a certain number of hours, in an atmosphere properly renewed, the symptoms due to its presence will be dissipated. If, on the contrary, substances enter the interstices of the different organs, without taking part in tissue formation, they are even then very subject to be taken up by absorption and to disappear with considerable rapidity. Those which remain longer are such substances as penetrate into the histological elements themselves, that is to say, into the fundamental substance of these elements.

What causes the length of the sojourn in the last case? Is it due to the longevity of the histologic elements? It is difficult to express a fixed opinion on this subject. We know that certain elements do not long resist. In the foetus the globules may be

in considerable proportion, and disappear with great rapidity. In 48 hours the proportion may fall from 900,000 globules to 600,000. I know well that these are conditions differing from the normal state; but it is well known that the globules are not long lived. But evidently solid histologic elements should last much longer, and it is highly probable that this is one of the reasons why remedial or toxic substances make so long a sojourn in the economy.

It is probable, also, that the degree of solubility or insolubility of a substance has a marked influence on the prolongation of its sojourn. We have just seen that metallic substances may have a very long sojourn. Thus individuals submitted to the nitrate of silver treatment never become completely white, and live often many years having the same coloration of the skin.

You may also take a substance intermediate between this state of absolute insolubility and a state of very great solubility; if you have a substance of semi-solubility, it is evident that it will be difficult to return such substance into the circulation.

It is probably thus that iodide of potassium acts; this drug having been recommended by Natalis Guillot and Melsens, to bring back into the circulation an enormous proportion of arsenic, when for several days this substance has no longer appeared in the excretions. Perhaps it promotes the solubility of the arsenical substance, which can be thus eliminated. Nevertheless, there is another manner of interpreting these phenomena; iodide of potassium possesses the remarkable property of promoting denutrition, of thus diminishing swellings, hindering production of hypertrophies, reducing hyperplasia. It is thus that iodide of potassium renders such great service in all hyperplastic affections, and in that affection particularly remarked for inducing hyperplasia, syphilis in its third period.

I have maintained that iodide of potassium, causing disintegration of remedial agents, should be considered as rendering denutrition more active, favoring the general round of nutrition, aiding in the disposition of the matters thrown off during the nutritive activity of the histologic elements; that is to say, those

substances having undergone regressive changes, and at whose expense urea and uric acid are formed, and at the same time aiding also to dispose of the mineral substances which have made a part of these elements for a period.

There is, then, a chemical and physiological manner of interpreting this action of iodide of potassium; but I place both one and the other before you with great reserve, as there is no true experimental basis for either view.

That which N. Guillot and Melsens saw has likewise been observed by everybody; the drug causes the medicaments to re-enter the circulation; but there are two possible explanations of the fact; the one which they have given and that which I propose to you.

There is another point of view under which we should consider the subject. We have just spoken of the duration of the sojourn in the tissues; it remains now to consider why certain of these substances appear so speedily in the excretions and others are so long delayed. How does it happen that one substance in the bladder or stomach undergoes absorption and appears, sometimes after three minutes, in the saliva or in the urine, while another, under the same conditions, will not appear for a day or for forty-eight hours?

This rapidity or slowness of appearance of substances used as medicaments is due to various causes. In the first place, the organ or tissue in which the substance is located is not without its influence. It is clear that a substance which has an affinity solely for the histologic elements, and penetrates into these elements, can appear in the secretions only after a lapse of time. But when substances are arrested almost on entering, when they are simply carried on in the circulation and penetrate the meshes of cellular tissue, or the cellular interstices of the tissues, then it is less difficult to understand how certain substances appear so speedily, and others so slowly in comparison.

There are two principal causes which govern this rapidity or tardiness of appearance in the secretions; the first of these causes is the tolerance of the system for the substance; the second is the

quantity of the substance present at one time in the economy. The tolerance is in relation to the nature of the substance, and we will explain what is meant. It is not through its mineral or vegetable nature that a substance acts; it is whether it may be of a homogeneous or heterogeneous nature as regards the organism. Thus Fourcroy has the priority in saying (I think he was the first to make the observation, though it is so long ago that I speak from memory only), that the soda salts should be accepted with more facility by the organism, as they exist in all the tissues in great abundance.

I have myself written (I ask permission to cite myself; it is long enough ago to have become historical): "It may be held as a general rule, that medicaments are ejected with so much the more rapidity, the more they differ from the principles which normally constitute the organism. Thus the potash salts, more heterogeneous in the blood than those of soda, are tolerated with greater difficulty in this liquid, and are sooner ejected from the economy."* These assertions, or this law, is exceedingly clear.

That which I wrote at this period has been amply verified, and experiments on animals, as well as observations in the human subject, have demonstrated the truth of the assertion.

Thus, our great physiologist, Claude Bernard, has shown that the soda salts are much better tolerated than those of potash.

Further experiments, repeated by a number of physiologists and chemists, have shown that this is a general fact concerning the soda salts in all the animals on which experiments are made in the laboratory.

This same fact concerning the toxic effects of the potash salts has been shown by different chemists, and Guldman has even demonstrated that the salts of potash render slower and enfeeble the cardiac contractions. It is on this account that they have been considered to have a toxic effect on the muscles. But this only expresses the fact, without explaining it. Why should this be so? It is because there is potash in the muscles, and for

* Gubler, "Commentaires Thérapeutiques du Codex." 2d edition, Paris, 1874.

this reason these salts are attracted toward them. And, finally, there is such a quantity present that there results a marked excess, which acts in opposition to the regular progress of nutrition and denutrition in the muscles.

The same facts may be observed for other substances: thus, the chlorides are better tolerated than the bromides, and these, again, better than the iodides. It is always for the same reason; there is abundance of chloride of sodium in the organism; on the contrary, no bromine, or very little, is present; it is the same for iodine. I do not say that it is impossible to find these elementary bodies in the organism; and certainly more would be found if vegetables containing these principles were made use of, for the minerals found in the organism but show the manner in which it is nourished.

I am convinced that in an inhabited planet containing manganese, more of the metal would be found in the organisms of the inhabitants than iron. In our planet iron is the predominant metal, and the salts of iron are better tolerated than those of copper. Again, there exists a very curious fact, interesting for the physiologist and the therapeutist, which is that the glucose found in the urine is much better tolerated than grape sugar. Very instructive experiments have been made on this subject, which lead the way to more profound study regarding the action of medicaments and poisons, and illustrating, also, the manner of undertaking this study from a chemical point of view.

Thus these two forms of sugar—grape sugar and diabetic sugar—are identical from a chemical standpoint. They are constituted of carbon and hydrogen in the same proportions. Yet when Claude Bernard injected diabetic sugar into a large dog, and observed what happened in the urinary secretion, he did not find any sugar appear in the urine; on the contrary, when he injected twenty grams of grape sugar into the same dog, he remarked that the dog instantly became, for the moment, diabetic, sugar being found in the urine.

This experiment has been repeated in various ways and has always given the same results.

It is evident that diabetic sugar is, as might be said, tolerated as a normal element, while grape sugar acts as a foreign body.

You can thus see that the tolerance or intolerance of the economy for a substance may be explained by considering whether the substance is homogeneous or heterogeneous as regards the organism which receives it.

How is this more or less rapid elimination explained, if we put aside influences above mentioned which control the duration of its sojourn? Here are the elementary phenomena, to which may be reduced the modifications offered by various substances: Three orders of facts are observed. There is, as you have just seen, absence in the secretions of the substance introduced into the organism, or, on the contrary, it appears in the secretions These are two absolutely contrary phenomena, remarked often when the tolerance for the substance is extreme or the intolerance very marked. Or there may be more or less rapid appearance of the substance. Thus, sometimes the substance is wanting, or is in the latent state in the economy; nothing in the secretions, no modification is revealed; or, on the contrary, it appears in them more or less speedily. And, appearing thus with more or less rapidity, it causes more or less irritation in the organs of secretion.

Again, another phenomenon is observed under these conditions; more or less excitation of a secretory organ, causing hyperæmia through hypersecretion. In other words, the substances introduced into the economy and eliminated therefrom may determine either (1) a very exaggerated secretion, or, (2) they may produce hardly any effect on the organ, or (3) the elimination occurs in a more or less lengthened period of time. I am about to give you examples of these various cases.

As examples of the non-appearance or the rapid appearance, I have already instanced diabetic and grape sugar, substances which appear to be similar, but which, in reality, differ widely as regards the living organism; that is to say, that notwithstanding their being of the same composition, they have different dynamic properties.

As examples of the greater or less rapidity with which substances appear in the secretions, there are some, as iodide of potassium, which appear after three or four minutes. Thus, in experiments made on the bladder, not in the normal condition, for then it does not absorb, but when in a morbid state, with ulcerations, consequently in excellent condition for absorption; in such experiments by Ségalas, and Demarquay, it was found that iodide of potassium injected into the bladder appears, after three minutes, in the saliva. Consequently, if you take into account that a minute is necessary for the substance to make the round of the circulation, you may see that absorption took place with extreme rapidity. Four or five minutes is a delay which is rarely met with, even when the substance is introduced into the stomach. Bromide of potassium is eliminated less speedily, in ten, twelve, or fifteen minutes. And, take notice, that these are two salts which resemble each other very much; but they differ not by any dialysable property not in their constitution; it is always potassium and a metalloid; but one is more heterogeneous than the other. Chlorate of potash is eliminated more slowly than bromide of potassium, but not always; sometimes the latter takes more time.

Again, the corresponding soda salts are slower of elimination in a notable degree. Thus, if you take iodide of sodium, or bromide of sodium, they are delayed twice as long in the system as iodide of potassium. It is the same for carbonate of sodium, as compared with carbonate of potassium.

Practical conclusions can immediately be drawn from these facts. If you wish to exercise a topical action on the emunctories, to which salt will you give preference, to soda salts, or to those of potash? To a substance resembling those present in the economy, or those differing from them? You will evidently make use of a heterogeneous substance, and consequently of potash salts, if your choice lies between the salts of potash and those of soda.

Again, observe what happens with diuretics, as the nitrate of potash, silicate of potash, the bromide of potash, even, a diuretic that I have utilized in the Beaujon hospital, and which is

appropriate for a certain class of subjects in whom the kidneys are irritable. These potash salts are more diuretic than the corresponding salts of soda.

The nitrate of soda and acetate of soda have been employed; these would be low-priced diuretics, but have not the value of nitrate of potash.

To compare the bicarbonate of potash with the bicarbonate of soda; the first is powerfully diuretic. If you take even mineral waters which contain a considerable proportion of carbonate of soda, with little potash, they will be more diuretic than others which contain much more of the two salts, but chiefly of bicarbonate of soda. If, for instance, you take the waters of Vals, containing five or six grams of bicarbonate of soda, you will find them less diuretic than the waters of Vichy, which contain five or six grams of bicarbonate of soda, and fifty centigrams of bicarbonate of potash.

If you wish speedily to render the urine alkaline it is to a potash salt that you will give preference, because it is that which causes the urine to pass more rapidly, excites more the renal secretion, causes a greater proportion of the salt to be found at one time in the organ which eliminates it, and, consequently, in the urine. Something similar may be said of the chlorate of potash as compared with the chlorate of soda; it is unfortunate that the former has so little solubility. Chlorate of soda presents a considerable degree of solubility as compared with the potash salt, but it does not produce the same effect on mercurial stomatitis, and particularly on ulcero-membranous stomatitis, which is so speedily modified by chlorate of potash. It does not produce the same effect, because it is very slowly eliminated; to produce a considerable modifying action, like chlorate of potash, it would be necessary to introduce it in very large doses. If, on the contrary, you wish to exercise a profound modifying action on the economy, if you wish to produce alterative effects, which I have styled metatrophic, an opposite course must be pursued; heterogeneous substances must not be used, for they, it might be said, incite the organism to rebellion: from their nature they

necessarily undergo rapid elimination. Preference must, then, be given to soda salts above potash salts always, when it is possible. It is preferable at all times to introduce into the system compounds which differ the least from the elements of the living tissues.

You will have to establish the inverse rule as regards the iodides, the chlorides and the bromides, and give the preference to the chlorides for the introduction of a metallic substance, rather than to the iodides. If you wish to increase the rapidity of the denutrition, to render secretion more active, to induce greater activity in the excretions, then the iodides should be brought into play. Of how long duration is the process of elimination of these various substances, some homogeneous, others heterogeneous? Just as heterogeneous substances appear most speedily, so they are most speedily eliminated. These are two facts which go together; for instance, if we take iodide of potassium, which is more heterogeneous than the bromide, in a few hours all is eliminated; and in a greater number of hours the bromide, also, will be almost completely eliminated, so that it will be difficult to demonstrate its presence. When chlorate of potash is used, it is partially transformed into chloride of potassium, and not less than thirty-six or forty-eight hours are necessary for the elimination.

But there is one singular fact in the history of medicaments; it is the almost constant direction that each one follows. Why does a medicament follow almost invariably the same route of elimination? one the respiratory organs, another the biliary apparatus? For a long period it was considered sufficient to simply observe the fact in an empirical way. I have thought that it might be possible to introduce a physiological reason which casts considerable light on all these phenomena which are of very difficult interpretation, and I have remarked: elements introduced into the system from without follow the route where similar elements exist in the economy, or of analogous substances, if any analogous elements are present. I am about to show you that this view is verified in all the several cases, and that it permits us to

foresee by what avenue any remedial substance which you have introduced will escape.

We will, if you wish, pass in review the principal secretions. The saliva and the pancreatic secretion contain the neutral salts, a little chloride of sodium and a small quantity of soda. The bile contains soda, it contains various fatty matters and the fat taken with the food, for margaric and oleic acids have been found in it, without considering the various substances peculiar to the bile, choleic and cholic acids, and many others. In the bile there is found also resinoid matters, a pigmental substance possessing varied properties, so that it has been divided into a certain number of chemical principles. Hæmatoidin is often found in considerable quantity in old cysts of the liver. The sweat contains much water, carbonic acid, volatile fatty acids, and acetic acid; with these it contains neutral salts, a small quantity of urea, and of uric acid, in individuals whose systems are overcharged with these products.

The urine contains much water, neutral salts, and acid in a free state, a small quantity of fatty matter, of which I have demonstrated the presence; and also, in a certain number of cases a ferruginous pigment.

Milk contains sugar, fatty bodies, mineral principles, neutral salts in great quantity, and an albuminoid substance.

We will reconsider the various secretions, and take up one by one the consideration of the substances that we find necessary to introduce into the economy. We often introduce alkaloids, we introduce saliﬁable substances, or neutral salts. By what route will these substances be eliminated? By almost every emunctory, since you see that almost all the secretions contain neutral salts; consequently, the salified alkaloids pass by all the organs of excretion. Nevertheless, there are routes more particularly followed by the various series of alkaloids. Those which are fixed pass rather by the kidneys, those which are volatile by the respiratory organs. Thus conine and the alkaloids of the umbelliferæ pass by the organs of respiration.

If you wish to have the action of the substance at the moment

it leaves the system, it is better to introduce into the circulation volatile substances which take the respiratory organs as a route of excretion.

Although the neutral salts are eliminated from all parts, there are, however, certain routes of issue always wide open; for instance, the urine and the neutral salts pass almost entirely in this fluid. And I would assimilate with these neutral salts other substances, as the resins, and the cantharidate of soda, which is transformed into cantharidin, and passes with the neutral salts in the renal secretion, thus producing the disorders with which you are acquainted. Let us take, as examples, the metals and the metalloids. By what route will they pass? I have shown you which organs or tissues in the normal state contain iron, and iron is the only metal normally present.

It is probable, however, that if manganese or copper were administered by kilograms, these metals might be found in the blood, but nothing is known concerning such a case.

The metals, then, follow in elimination the route by the bile and the urine; by the bile in particular, because in the bile there is still more ferruginous pigment than in the urine.

You can see how generally this rule can be applied, how it assists the memory at the same time that it strikes the mind.

We will make an application of the rule to arsenic. It escapes particularly in the bile, so much so, that when there is but little in any other organ, it is there that it should be sought; and not only in the hepatic parenchyma, but also in the flow of bile.

This fact has been demonstrated in the experiments made at the physiological laboratory of the Faculty by MM. Laborde and Bonnefoy. I repeat, that when small quantities of arsenic are introduced into an animal, it should not be sought elsewhere than in the bile. You see that it is very important to be acquainted with this rule, which suffers certain exceptions, but these exceptions themselves have their origin in other rules, as I will attempt to demonstrate to you.

Fatty matters are excreted in the bile, the milk, by the seba-

ceous glands, and in small quantity in the urine. Resins are eliminated in the bile, where considerable quantities are found. And remark this: a large number of resins are cholagogue. A great number are drastic purgatives, because they act on the mucous membrane of the digestive tube and provoke symptoms of hypercrinesis; but when not very considerable doses are employed, which do not produce their effects until long after their introduction into the primæ viæ, they owe their late action to having been secreted by the liver, eliminated by the bile, and arriving then in the intestines, produce their usual effects.

By what organs are the acids eliminated? We have seen that two liquid secretions are acid: the sweat, the principal one as regards the acids, and then the urine. Thus, it is a method among the vulgar in the North, and in many places (the manner alone differs), to plunge a red-hot iron into a mug of beer; the iron induces ebullition, which leaves the beer slightly soured (I have tasted it; I found it disagreeable, but it is considered delicious), and thus drank, while heated, it induces abundant perspiration. Where wine is common in a country, wine thus rendered sour is used.

Is it not curious that, by considering the rules of applied physiology, we, in the end, understand the vulgar methods of treatment which physicians ridicule when they do not understand? Thus you will no longer laugh at this practice when you are aware that acetic acid is eliminated by the sudoriparous glands, excites the secretion of these same glands, and determines irritatation and redness. The acids are also eliminated by the renal glands, so that by introducing into the economy phosphoric acid the acidity of the urine may be augmented, and urines of neutral reaction rendered acid.

CHAPTER XXVII.

Elimination of Medicaments (Continued).

Influence of different doses; practical applications.
Under what form substances are eliminated, intact or more or less transformed.

GENTLEMEN:

It is necessary for me now to speak concerning the influence of the quantity taken on the rapidity of elimination.

When heterogeneous substances are considered, that is those which are not analogous to the principles present in the economy, a very small dose may possibly be tolerated; it passes, as might be said, unperceived. Suppose ten centigrams of iodide of potassium be taken; there will be no increase in the renal secretion and no appearance of iodide in this liquid; but just in proportion as the quantity of the substance augments, the rebellion of the various organs increases, for they take up the medicament only to reject it with great energy. And in such cases you will have almost instantaneous appearance of the active substance in the products of secretion. It is thus, when you introduce a gram of iodide of potash, that very promptly, say after three or four minutes, it is found in the urine.

Consequently, you can see that the dose has considerable influence as regards the tolerance of the economy for a medicament. And this explains why, when a considerable dose of a substance is introduced at one time into the system, during the first of its action, say during a few hours, considerable quantities of this substance are eliminated, while, on the contrary, what remains will require a much longer period for elimination. You will have seen half the iodide eliminated in the first three or four hours; the second half will require the following twenty-four hours.

Take sulphate of quinine; many physicians give fifty centigrams at one time. When these large doses have been introduced, the medicament appears in the urine after twenty minutes, and much passes during the first four or five hours; then elimination becomes slower, and finally, the third day, a certain quantity of the alkaloid is yet met with in the urine, but is found to be in very small proportion, and the elimination is prolonged in a manner which would not have been expected if we were not acquainted with the law that elimination is more rapid in proportion as the quantity of the substance saturating the economy is more considerable.

The homogeneous substances, on the other hand, can be tolerated in pretty large quantity; it is only when the dose is enormous that they commence to be eliminated. Much chloride of sodium can be injected before it manifests its presence by an excess of chloride in the urine, but a moment arrives when its excess in the system will be shown by the passage of a larger quantity in the urine. It is the same for sugar. You know what happens for individuals predisposed to diabetes: if they eat a moderate quantity of sugar, there will be no notable effect produced on the urinary secretion; if they eat substances containing considerable proportions of sugar, the contrary will be the case.

The same holds true in albuminuria: if the patient eat, as did Claude Bernard, twelve hard-boiled eggs, albumen will be found in the urine.

In the same way those who eat candies in large quantities may, for the moment, become diabetic. But, I repeat, it is only when the dose of a homogeneous substance is enormous that it is seen to pass into the secretions with rapidity.

The practical inference to be drawn from what I have said regarding the quantity of active principles ingested as remedial agents, can be stated as follows: if you wish to determine topical effects on the various emunctories, it will be necessary to employ substances very different from those found in the economy, and to employ them in large doses at a time.

If you wish, on the contrary, to produce effects through the

diffusion of the drug in the economy, and particularly alterative effects, that is, if you wish to modify in a slow, sustained manner the living economy, it is necessary to employ substances resembling as much as possible those normally present, and to employ them in small, repeated doses for a considerable period of time. It is possible, no doubt, that with heterogeneous substances, employed in very small doses, you may find sufficient tolerance to produce metatrophic effects; just as with large doses of a homogeneous substance you can determine topical effects on the emunctories. But the reunion of these two conditions—a heterogeneous substance in very large doses, to produce topical effects, a homogeneous substance in very small doses, to produce general and alterative effects on the system—these are the conditions it is necessary, if possible, to realize. And examples demonstrative of the truth of this statement could be brought forward. Thus, for instance, mercury, if employed as iodide of mercury, will necessarily give rise to many phenomena during its excretion; it causes salivation and symptoms of stomatitis in the mouth and gums. On the contrary, chloride of mercury is a substance which does not affect the mouth, and which does not induce the phenomena during its excretion observed with metallic mercury. You see that interesting applications could be made.

Again, you are all aware that one of the advantages of mineral waters is to produce slow but profound effects, modifications analogous to those produced by alteratives. The mineral waters give with most facility all the symptoms induced by trophic changes. In the paludal cachexia observed in swampy countries you make use of the mineral waters, that is, of solutions which do not contain active principles in large proportion, and which, being taken for a considerable period determine, in the end, very extensive and very profound general phenomena. I restrict myself to these general considerations, which appear to me sufficient to establish the importance of the distinctions which we have indicated. In considering the various routes of elimination I passed in review the neutral salts, the metals, fatty substances, the resins, the acids, and I demonstrated that, through

physiological indications, the organs selected by them for elimination could be determined in advance.

In order to terminate this enumeration, it only remains for me to speak to you concerning gaseous substances and volatile principles, that is, gases and substances in the state of vapor.

What route can you assign, in advance, for the elimination of volatile and gaseous substances? The organs by which they are eliminated are all indicated; they are those by which escape principles of the same species: the respiratory organs, on the one hand, the sweat glands on the other. These glands, acting in conjunction with the organs of respiration, give issue, not only to volatile substances, such as the fatty acids, but even to sulphuretted hydrogen and to carbonic acid. At the same time these glands take from the atmosphere the gases which compose it, and in particular oxygen, which afterwards serves to keep up respiratory combustion. I do not say that this phenomenon is very marked, but it is notable. It is by these two avenues that gaseous and volatile substances escape. In this way are eliminated carbonic acid, sulphuretted hydrogen, phosphoretted hydrogen, and also compounds derived from it, most essential oils, as also the camphors properly so called, originating from the labiatæ and compositæ, alcohol, and a number of substances equally volatile, ether and many anæsthetic compounds and volatile alkaloids. These are all substances eliminated particularly by the respiratory organs and by the skin, or, at least, by a part of the cutaneous glands.

I repeat, experiment demonstrates this; but the general law formulated above would have enabled you to predict that this double route would be followed by gaseous and volatile substances. I now make a few applications to therapeutics. If you wish to excite urinary secretion, will you have recourse to volatile or gaseous substances? No; but you know by what organs urea and all the neutral salts pass, and also the salifiable substances, and the acids capable of taking soda, and thus forming salts in their passage, and urea itself, and cantharidin. These substances pass out by the urinary organs, and conse-

quently these are the substances which will serve to excite the secretion of the renal glands.

To excite biliary secretion you will have recourse to the resins. Most of the resins are drastic substances, which pass by the liver; once there, they provoke biliary secretion. So, also, do the metals and metalloids. I have even recently cited to you new experiments which prove clearly this property of the metalloids, and of arsenic in particular, which approaches very closely the metals, and is hardly distinguishable from antimony. These, in effect, are the substances which most energetically provoke biliary secretions.

Salivary secretion will be provoked by the neutral salts; especially by chlorate of potash.

To excite cutaneous secretion you will recommend volatile substances. As a rule, when fatty acids are contained in the aliments, as in cheese, there will be excitation of the skin. This kind of aliment should, then, be proscribed when treating irritative cutaneous affections. You may also employ the gaseous substances when proper. You will excite lacteal secretion by the feculents, sugar, fatty bodies, by aromatics even; it is by the skin that substances of this order are eliminated, and milk itself owes a portion of its qualities to the aroma it presents. This is so true, that milk of excellent quality, as regards chemical and microscopical composition, is not well tolerated by infants in a certain number of cases, and other milk, of less beautiful appearance, seeming not so rich, but good as regards the form and small size of the globules, will be better tolerated if presenting a peculiar aroma.

You see that these rules become more evident as we advance, and more important.

Let us suppose that you wish to modify a catarrh of the organs of respiration, and the state of local irritation which exists in a certain number of affections. To what remedies will you have recourse? To aromatic substances, but which are also volatile. Thus, you will employ the essences, and among the essences those which cannot be brought to the state of resins.

Here there is something interesting to say; that is, that the non-resinifiable essences are probably oxygenated essences. Thus, take the camphors; they do not undergo oxidation, they are oxygenated. There are liquid camphors, such as the essential oil of cajaput and the essence of eucalyptus. These essences which are oxygenated do not undergo any oxidation, or very little, and thus pass almost intact by the respiratory organs. And if you wish to act on these organs, it is to them that you will have recourse The other essential oils are not completely burned, but they are in great part consumed, and particularly the spirits of turpentine and Canada balsam. These essences become resinified with extreme rapidity, as also the balsam of copaiva, and thus they are good solely for the urinary passages.

If you have to deal with troubles of the sensibility of the organs of respiration; if you wish to modify a cough; to what species of narcotics will you have recourse? You should give the preference to the volatile narcotics, which will act first on the nervous system, and locally where they are eliminated. So the alkaloids furnished by the umbelliferæ are preferable to the others, because they have a greater faculty of volatilization. You can see what benefits are obtained from syrup of belladonna in hooping cough. You see also what good results are given by plants of the family of the umbelliferæ, such as the *phellandria aquaticus*, which has been considered by Sandras as a sort of panacea in chest affections; it modifies the morbid sensibility in such cases. I shall say as much for conine and conicine when we have in France pure products, analogous to those obtained by Christison. Do you wish to act on a catarrh of the urinary passages? you will have recourse to analogous substances, but having different qualities. Thus, you will employ precisely all the essential oils which are rapidly resinified, and which, passing to the state of oxides, combine with the acids and become true salts; you will administer them in preference, because they will pass, in large part, by the urinary passages.

It is on this account that copaiva enjoys so much celebrity in catarrh of the bladder and urethra. It is on this account that

Canada balsam is also a good remedial agent, while hardly any effect is produced in these cases by eucalyptus, the essential oil of myrtle, or by the other oils which might be considered as liquid camphors. If you wish to produce narcotic effects, you will have recourse rather to the fixed than to the volatile alkaloids, to morphia rather than to atropia, or other alkaloids originating from the umbelliferæ.

One word on the changes which remedial substances undergo in their passage through the emunctories. The nature of these transformations is little known. It is very probable that a part of the changes formerly supposed to take place in the blood are really produced in the organic tissues, or in the passage through the emunctories. But we can but suppose this to occur, the fact has not been demonstrated.

At the moment the substance escapes from the blood to penetrate into the organs of elimination, just then it becomes separated from the albumen. This is a primary modification. It happens also that in the secretions, where the foreign substances are mixed with other principles normally present, they encounter acids which set them free—exactly as phosphoric acid causes uric acid to pass into the free state; this is just what happens for a certain number of substances eliminated by the renal passages. When the substances are constituted of metalloids having no great affinity for their bases, these metalloids may be set free; and this happening when patients take iodide or bromide of potassium, a physician with a finê sense of smell may detect the odor of iodine.

The same thing happens for unguents containing iodine and lard; they become brown, and exhale an odor of iodine. In the respiration it is the carbonic acid which causes the liberation of the iodine in a way to determine a very evident odor of iodine for a person having a very delicate sense of smell. I have already said that substances follow a passage determined in advance, and that this passage is the same as that followed by analogous or similar substances. There are circumstances under which this rule suffers very notable exceptions; substances

usually following a certain direction no longer follow it, and others are forced to pass by certain emunctories where they were not expected to appear.

These are very interesting facts, with a certain number of examples of which I am acquainted. Very probably these facts are more numerous than is generally supposed at present, for from time to time I discover a new example.

I have shown that the bromhydrate of quinine does not induce the toxic effects, the quinic intoxication, produced by sulphate of quinine, and it is highly probable that it does not act upon the auditory nerve.

On account of this observation, foreign physicians, in England and at Vienna, have had the idea to give bromhydric acid in solution, concurrently with sulphate of quinine· and they have remarked that under the influence of the bromhydric acid thus present in the economy, though it had not been combined with the quinine, the phenomena of quinic intoxication habitually observed do not present themselves; as if the acid had given its veto and prevented the sulphate from producing the phenomena of Menière's disease. This would be a very curious fact if it were verified, but I am obliged to question it, because I have not yet succeeded in establishing the reality of this phenomenon. It has been asserted by certain foreign practitioners, but in general we have more confidence in what we ourselves observe; and on this account my opinion on the matter is subject to a certain reservation.

But here are other examples: it is certain that the presence of camphor in the circulation prevents cantharidin from producing its ordinary effects on the urinary apparatus. That is to say, that if camphor is internally administered, there will be less of those phenomena of cantharidism affecting the kidney and bladder than under different conditions. This is what experience has demonstrated. But I do not mean to say that camphor applied on a blister is a good practice. It is, if you wish, a means of preventing cantharidism, but it is because the camphor thus applied opposes the action of the cantharidin, and that the

greater the quantity of camphor the less the effect produced by the blister. I desire, then, to dissuade you from the idea of employing camphor as an application to the surface of the vesicating plaster. But it is entirely different when the camphor is introduced by the stomach, or by inhalation; then it is a practice to be commended. It has been a mooted question as to how camphor opposes the passage of cantharidin into the urine; probably a sort of combination occurs between camphor and the active principle of cantharides; but camphor does not pass by the kidneys. Thus, considerable quantities may be introduced and none at all found in the urinary passages. On the contrary, camphor is exhaled by the respiratory organs and by the sweat glands And, as it does not pass through the kidneys, it opposes the passage, by these organs, of other substances with which it is associated. But, in this instance again, I am obliged to say that it requires further study to determine whether this interpretation of the phenomena is correct.

I present another fact of a different order, which is very interesting. You give a subject iron, under no matter what form; you give him a soluble iron salt with the vegetable acids, or mineral acids, or perchloride of iron, or tartrate of potash and iron. You will find no trace of iron either in the salivary glands or in the products of their secretion. On the contrary, you find that the first route taken by iodide of potassium is to pass by the salivary glands; it passes also by the urine. But a curious fact: when iron is combined with iodine, when iodide of iron is given, or when you give a ferruginous solution containing iodide of potassium, you will find iron in the saliva; the iodide has compelled the iron to pass by this route.

These facts are very interesting, but are little known; it is to the future and to you that researches on this subject belong. I have given you a few examples; they are sufficient to demonstrate the reality of the facts. It seems that if they were more numerous and better known, if they were better classed, if the interpretation I have given is just, one could know in advance how to associate substances in order to force them to pass by any

direct route, and prevent them from passing by the organs they generally traverse. You can see that there would be a practical interest in the knowledge of such facts.

Substances introduced are eliminated in greater or less proportion, but they are never found completely unchanged in the emunctories, or in the products of secretion; ordinarily there is a certain proportion wanting. Is this due to the imperfection of our means of finding active substances, or is a portion of the substance destroyed in the economy? Both suppositions are well founded. It is very difficult to find even mineral substances in the products of secretion.

We know that a small quantity of mercury or a small amount of lead may pass in the urine; nevertheless, a certain number of chemists, having analyzed these secretions, in order to determine if they contained a more or less notable quantity of metals which they knew had been introduced into the system, have not been able to demonstrate their existence in the secretion.

Consequently, it is impossible to study the form under which these substances are eliminated. But there is one consideration of importance; physiological laws demand that a certain portion of the principles introduced be altered, modified, or even more or less completely destroyed. There are three principal categories of facts bearing on this point.

When we have to deal with very stable compounds, particularly with mineral substances, sometimes even with organic principles, or when the affinities are very feeble, the substance may pass absolutely unaltered. It is found just as it is introduced.

Another case: when the combinations are very unstable, when we have to deal with organic, rather than mineral substances, if the affinities are very powerful, it will happen, on the contrary, that the greater portion of this substance may be altered, modified in various ways, and more or less completely destroyed.

Finally, there are intermediary cases, where, with a certain degree of affinity, the substance may be in part altered and in part unaltered.

I will pass in review the various categories of substances belonging to these three groups.

To commence with, I will speak to you of substances which pass unaltered, or almost intact. These are the carbonates, the nitrates, the sulphates, the silicates of potassa and soda; that is, the alkaline salts. These salts pass absolutely without alteration. The sulphate of protoxide of iron passes completely unaltered, contrarily to what might be believed, while the sulphate of the peroxide of iron is reduced. The yellow ferrocyanide of potassium passes unaltered, while the red cyanide passes to the state of yellow cyanide. The sulpho-cyanide passes without alteration, as do also alum, the chlorides, the bromides, and the iodides.

There are even organic substances which pass without alteration; thus, the principles which give their distinctive colors to indigo, to rhubarb, to gamboge, to the resins of the coniferæ, of the terebinthenaceæ, and of the leguminous plants, as the resin of copaiva; sulphuric, nitric, chlorhydric, and phosphoric acids, also pass unaltered.

There are also certain organic principles which enjoy the singular property of passing through the economy without alteration, being found almost intact in the secretions.

No scientific experiments have been made to prove this, but you will see that the stories recounted by travelers and physicians are sufficient to establish it. There are substances so slightly altered that the products of the secretion of individuals who have taken them are capable of inducing the effects produced by alkaloids themselves. Thus you are, no doubt, familiar with the species of false mushroom, which is covered on its surface with white spots. This species of false mushroom contains an alkaloid which is a poison of great energy. I have, nevertheless, eaten it, in order to know what effects would be produced; and I am obliged to say that in certain cases I have remarked disagreeable gastro-intestinal effects ensue. But it is, at the same time, a substance capable of inducing intoxication, producing a drunken state comparable to that induced by alcohol or tobacco.

In barren countries, as in the most westerly parts of the Old World—that is, in Siberia, and as far as the vicinity of Kouriles—there are vast extents of territory where substances capable of inducing intoxication are wanting, and where this species of false mushroom is considered as something delicious. In these countries this false mushroom is employed to produce intoxication. All the tribes inhabiting that territory eat this mushroom, and prepare a liquor in which this substance enters largely. But a strange story which has been recounted by observers worthy of belief, is that when an individual has rendered himself drunk with the false mushroom, and passes urine impregnated with it, there is never wanting an amateur near him who collects the liquid as it passes, while yet warm, and renders himself drunk with it. It would even appear that four or five persons have passed, one after the other, partaking of the pleasure without having undergone the trouble, that is, getting drunk without being obliged to manufacture this famous intoxicating liquor.

These facts, observed by travelers, are very interesting as presenting such evidence of the unshaken fixity of certain substances, even of organic nature, which not only pass through the economy without having left anything of their substance, since what has intoxicated the one can, after its passage, render another drunk, but also without having undergone any alteration. There are other substances which, in passing through the system, undergo partial modification, but of which a part also passes without alteration. Then again, there is a third category of substances which are, in great part, decomposed and destroyed. But it is necessary to make a distinction, as regards the modifications undergone by substances, into two groups: sometimes substances undergo only isomeric modifications, as I have said to you when speaking of quinine, which passes in the state of quinidin or quinicin; sometimes there are the different modifications which I have described, these combinations with new principles, these copulations, when acids are formed at the expense of an essential oil, as, for instance, of glucol. Again, there is splitting up of

substances, and true reductions, which are the same as the division or splitting up of substances through oxygen.

Quinine, for instance; for how long a period was it believed that it underwent no alteration and could be found intact in the secretions?

I leave these facts aside, to take up the oxidations. These oxidations carry the substance from the most inferior state of oxidation to the most advanced state—that is, until an organic principle is transformed into water and carbonic acid. And I would say the same thing when considering hydrogen. This body causes one organic substance to become sulphurous acid and water. These last alterations interest us at present, for they lead to the destruction of the substance.

I have said that there are substances which undergo partial, and others complete alteration. For instance, substances which are in part burned and in part remain intact; these are the essential oils, which are hydrogenated carbons. Those which are constituted at the same time by carbides of hydrogen and oxygen belong rather to the preceding category. They resist so much that they can be found almost in totality in the secretions. The sulphuretted essential oils are altered with facility; the sulphur becomes oxidized, as do also the essential oils, and they pass, in great part, altered and destroyed. The essential oil furnished by asparagus is an essence which is partly burned, and in part resists. The same may be said of oil of sweet almonds. Tannin, also, is in this category; it is a glucoside, producing at first gallic acid; here it becomes pyrogallic acid. Javel water is partly oxidized. And in this class alcohol might be cited. You know that there have been great differences of opinion as to the changes alcohol undergoes. At first, long ago, it was admitted that it underwent combustion and became finally water and carbonic acid. But Maurice Perrin, Lallemand, and others assert that alcohol traverses the economy without alteration; that it is found in the secretions, and that, consequently, the belief formerly held was pure illusion. Two classes of substances may be distinguished, and alcohol belongs to an intermediary series. The

conditions under which it undergoes alteration, or, on the contrary, remains unchanged, are easily understood. If very little alcohol is introduced, it will not pass unaltered. You will never observe the breath of an individual who has drank very little wine give the perfume of acetone or aldehyde. Consequently, small quantities of alcohol introduced into the system in a normal state are burned and disappear, while, on the contrary, if you introduce considerable proportions it passes, in great part, unaltered. It is under such conditions that a lamp might be made to burn with the alcohol of the breath. But these are conditions not observed during the hygienic or therapeutic administration of alcohol.

Truly can it be said "a Physician is one who throws medicines [illegible] he knows little about into [illegible] he [illegible]

CHAPTER XXVIII.

Elimination of Medicaments.

Oxidations in the economy.
Variations in the action of remedial agents.
Rôle of medicaments; rôle of the organism.

GENTLEMEN:

I will speak to you to-day of substances which are, in large part, burned, and which consequently are destroyed in the sense we give to the change, for we know that nothing is lost or nothing created, except as to its form.

There are certain substances which pass from the emunctories completely consumed, they are found in no appreciable portion, though it cannot be said absolutely that they are not at all present; as they may be found unaltered in exceedingly small proportion in the secretions.

I have said in the last lecture that sulphuretted hydrogen passes in part unaltered; it may be collected in the respiratory exhalations; there is, however, a certain proportion which passes into the state of sulphurous acid. But the sulphides of potassium and sodium are burned in much larger proportion.

There is also a general rule, discovered by Chevreul, applied by Woehler, and of which examples are known in therapeutics and hygiene, that is, that the presence of an alkali aids in combustion. Consequently an acid, which is not burned when free, will be more apt to undergo combustion if in combination with an alkaline base; thus, the sulphide of potassium burns with greater facility than sulphuretted hydrogen, and passes to the state of sulphate of potash.

The organic acids, when they are in the free state, burn some-

what, but imperfectly, and very slowly. On the contrary—as Woehler has demonstrated, and Mialhe has established by new facts—when these same vegetable acids are combined with alkaline bases, even with lime, but particularly with soda and potassa, they are consumed with extreme facility, are transformed into carbonic acid and water, and then, instead of the citrate or tartrate of potassa and soda in the urine, are found carbonate of potassa or soda. This explains the modus operandi in treatment by grapes, cherries and strawberries; these fruits have an identical action, in rendering the humors alkaline, with bicarbonate of soda or the treatment by Vichy and Vals mineral waters. These substances are almost completely, it may be said completely consumed, for they are never found in the state of citric or malic acids; but they are consumed slowly, more slowly for the last acids I have mentioned than for the first. The acid they most rapidly consume is the one normally present in greatest proportion, acetic acid; then comes citric acid and malic; but oxalic acid is consumed much more slowly, for it forms in the emunctories almost insoluble combinations with lime, from which results a state of inalterability not acquired by the other acids. Such, then, is the order in which these substances are consumed.

I shall now present to you a fact of the same order, concerning those powerful alterative substances which cause modifications through their nature alone. While tartrate of potash is consumed with so much facility that it is collected almost in totality as carbonate, on the contrary, it is found that the double tartrate of potash and nickel does not suffer combustion. The nickel prevents the combustion of the tartaric acid, even though it be partly combined with the potash. It is well to be acquainted with these facts, because they will certainly aid when the general laws are taken into consideration, in the comprehension of many processes which yet remain obscure.

But these two categories of substances, of which one series is partly consumed, and the others burned almost completely, form in reality but one species; combustion being established with greater facility in one series than in the other; there is no

fundamental difference, and a substance of the first series can be placed in the second, and vice versa, where we suppose that combustions are imperfect, by simply varying the doses introduced into the system. Take, for instance, alcohol, of which I have already spoken, but on which I wish to insist. This is a very interesting question, on which many dissertations, have been made; a very profound discrepancy exists between the different observers on the question, as to what becomes of alcohol introduced into the system. Certain observers, as you know, say that alcohol is a combustible aliment, aiding in respiration; that it enters into combination with all the ternary substances introduced as aliments, that is with the fatty and saccharine matters, which are assuredly the best substances for inducing combustion. Others, on the contrary, assert that alcohol passes without alteration; we have been able, they say, to collect it in the secretions.

Both positions are, as I have said, correct. The opinion of the first series of observers is correct for the remedial, physiological, or hygienic use of alcohol; the others say what is true when the substance is taken in actual toxic doses.

Thus, I have said to you, when a large quantity of alcohol is introduced, it passes, in great part, unaltered in the secretions, it is immediately found in the state of aldehyde.

On the contrary, where alcohol is introduced in very small quantity, in hygienic or physiological doses, it undergoes combustion sufficiently to become, probably, water and carbonic acid.

Consequently, as you see, the same substance may be placed in either or both of the two categories. The quantity of the active principle found in the secretions shows, then, only the difference between what has been introduced and what has been destroyed. And this difference varies necessarily in accordance with the conditions we have indicated; the combustibility, more or less marked, of the substance and its alterability; there are certain substances of which but a very small proportion is found in the urine, while of others ninety per cent. may be collected; such are the chlorate of potash and the sulphate of quinine, but this last, with the reservation I have made concerning it. Then there

are all the intermediary substances between these two extremes, of substances of which almost nothing is passed, and others of which almost the totality is found in the secretions. When these substances are examined as they pass in the secretions, it will be perceived that the principal changes they have suffered have been brought about by oxygen; they are oxidized; the others have entered into new organo-metallic combinations.

I have cited to you examples, many of which are familiar; substances which, introduced as hydrogenized carbons, or something similar, generally ternary substances, contract combinations with nitrogenized animal principles, which are in reality the waste matters thrown off by the tissues, with glycocol particularly; forming new combinations much more stable than a great number of the waste materials from which they were formed. And these new combinations thus formed carry off with greater facility, and become means of excretion for the peccant matter contained in the economy when it is saturated with principles not completely consumed, and which could not pass out.

Thus the first example of this kind is benzoic acid. It has been seen that it is transformed into hippuric acid. We know that this change results from the combination of the benzoic acid with glycocol. These facts are numerous, and it might be said that all the hydrogenized carbons, which are called essential oils, as those of turpentine and eucalyptus, are transformed partly into acids resembling hippuric acid. They are seen to pass in the state of nitrogenized combinations, and are thus rendered almost unrecognizable as regards their chemical and organoleptic properties. It is evident to me that these are the substances which give a peculiar smell to the secretions; when a person has taken the spirits of turpentine, Canada balsam, essential oil of cajuput, or balsam of copaiva, the odor resembles that of violets. But the odor of violets is not always obtained; sometimes it rather resembles that of melilot, or of vanilla. These are evidently acids formed by combination. But again, there are substances which are split up before passing in the secretions, reduction having taken place.

Finally, there are substances which appear to pass unaltered, and which are found almost in totality in the secretions, such as quinine, but which, nevertheless, have undergone certain alterations, difficult, it is true, to demonstrate, but becoming more clear when this substance has been introduced into a living organism, where it induces none of the symptoms usually produced by quinine, that is, where the substance is rendered inert.

Up to the present we have considered only the nature of the effects produced by remedial or toxic agents. But it is important also to seek an explanation of the circumstances which cause variation in the physiological and remedial effects. There are two principal causes for these variations of action: the first is the power of the agent itself, which varies in different cases and under different circumstances; the second is the ensemble of phenomena as regards the organism, and which may be expressed in one word: resistance of the organism.

The "peculiar power of a remedial agent" is not an expression having always the same significance; it does not signify that a medicament is always endowed with the same virtues and in the same degree, and that it can always exercise a calming or stimulating action. The peculiar properties possessed by the remedial agent are not thus in relation with the particular conditions of pharmaco-dynamic energy possessed by or inherent to it.

If we study the action of analogous principles grouped in the same substance or in a group of vegetables which act in the same way, here is what we observe: If we take alcohol, we remark, according to the experiments made by Dujardin-Beaumetz, that certain forms of alcohol are endowed with great energy, while others are tolerated with facility, and cause much less marked symptoms of intoxication than the first kind. Ethylic alcohol is, for instance, supported with facility by the human race, while amylic alcohol, from potatoes, is very poisonous.

If we take the poisonous solanaceæ we again fina a gradual descent in physiological action, descending from the strongest alkaloids, such as atropia and duboisia, to daturia, nicotine and solanine, which is the feeblest. But there are other analogous

facts. Very notable and often striking difference in intensity of pharmaceutic and dynamic action is observed in substances constituted in the same manner, or which are identical in all essential parts to substances which are said to be isomeric. These are metallic or metalloid substances which owe to their own peculiar nature, independently of their state of combination, their organoleptic qualities, and, consequently, their physiological action; here we find the cause of the modification in intensity of the physiological action to be the structure and dynamization of the substances. I will give you an example. Oxygen is an agent of combustion; atmospheric oxygen has qualities aiding in combustion with which you are all acquainted; it gives us the means of burning up our own tissues. But there is one form under which oxygen presents itself—allotropic it is termed—formed of three condensed molecules of oxygen, a form which presents enormous dynamization, so that it becomes a very energetic poison, and I have given you an account of some of the symptoms produced by it on myself.

For isomeric substances there are also great differences in intensity of action, such, I repeat, that it is not sufficient to know that the substances are isomeric to admit any identity of physiological action. No identity of action must be thought of before having really observed such identity. I have already spoken concerning the difference in action of the glucose of diabetes and that of grapes. Take, for instance, the isomeric substances obtained from quinquina; the same fact holds true; on one hand you have quinine, which is of great power; on the other quinidin and quinicin, which are inert. Again, cinchonidia is almost the equal, perhaps the equal of quinine, although there are not sufficient experiments to decide the question; while on the other hand, cinchonine and cinchonidine are inert. These substances are isomeric, but the molecular arrangement is different. In the series of caffeins, there are great differences between the caffein obtained from coffee and that obtained from tea, from the leaves of the mate plant, and from Paullinia. Thus, experiments which I have lately made show that these substances, which have

exactly the same composition, which for the chemist are identical, are substances which act differently. Thus, guaranine is much more active as a diuretic than thein or matein. Consequently, as you see here, again, in this group, it is necessary to take into account structure and dynamization of the substances, in order to explain their effects.

There are conditions of another order which explain the activity of remedial substances, their state of mechanical division, their state when about being formed, or nascent state, and finally whether they are in the free or combined condition. It is clear that it is not the same thing for a substance to be in combination as for it to be free to penetrate into the combinations which are offered to it when it arrives in the interior of the organism.

For instance, I will cite to you these facts: Sulphur is found in pharmacy, under two principal forms; the first is sublimed sulphur, washed or not; the second is precipitated sulphur, called milk of sulphur. Sublimed sulphur is dissolved with less facility; the other presents itself under the form of an impalpable powder, of pale yellowish color; it is almost white. But this last variety dissolves better, and consequently penetrates with more facility, by absorption, into the economy.

Arsenic is generally combined with oxygen, in arsenious acid, or combined with a base, as arseniate of potash or soda; these substances have greater activity than their conditions of solubility would lead us to suppose.

On the contrary, I have shown you, by a curious example, almost impossible of comprehension, that cacodylic acid, formed by methyl, in which a certain proportion of hydrogen is replaced by arsenic, and which contains fifty-four per cent. of arsenic, produces no effect on the digestive tube, and has hardly any poisonous action. It is probable that this is due to the very great resistance this substance offers to absorption, and I will shortly show you that analogous effects are obtained in a somewhat different manner by simply incorporating substances in inert matter. Besides the composition of the active substance, there is also the question of

quantity. It is easy to understand, and every one considers it as a fact to be taken for granted, that the intensity of the action of a remedial agent is in proportion to the dose given. But it is necessary to be reserved as regards this point, and I will cite examples where it would seem that the intensity of action was in inverse proportion to the dose. It is right for me to warn you that it is not the dose introduced at any one time, to be absorbed, that requires careful consideration, nor the quantity that may have passed through the organism, and which may be very large if introduced during a long period; what is of paramount importance is the quantity present at any one time in the circulation and in the parenchyma, and which consequently is in the state to act.

I agree with every one, what might, for that matter, be presumed in advance, that there is a direct proportion between the quantity of the active substance introduced into the primæ viæ and the effect it produces, with the condition that this substance be in favorable condition to act; but you will see that these conditions are not always realized, and this fact should receive careful attention when it is desired to explain the greater or less activity of substances from a certain dose. Consider, for instance, the solubility, which has great influence; the same substance may, as it is introduced in a soluble or insoluble state, produce no effects, or, on the other hand, act with great energy. Kermes and magnesia are in this category. For magnesia, it is easy to understand why this is so, for it does not act of itself; it is necessary that it be dissolved, that it become carbonate of magnesia, with excess of acid, in order to become active in any degree; generally it is transformed into acetate or into other salts, through the presence of acids of more or less energy.

Kermes (sulphuret of antimony) is somewhat less known. Physicians are often disappointed with an excellent preparation of kermes; they obtain effects so variable that many no longer use it. Kermes will act with great energy if you introduce an acid concurrently with it. If you administer it to a patient in

pneumonia, or in capillary bronchitis, and thoracic affections of gravity, kermes, given simply with a little gum water or any mucilaginous water, if there is no acid in the primæ viæ, will pass almost unperceived. If, on the contrary, you give at the same time some lemonade, or somewhat new wine, then the kermes will have considerable effect; even with no very considerable doses you will have effects approaching those of tartar emetic. Calomel presents analogous peculiarities. In general, it may be said, that when the conditions are favorable to absorption, the effects are considerable, while under contrary conditions they are insignificant or, at least, considerably enfeebled.

We will consider the conditions which render remedial agents more or less active under other circumstances. It is a question which will present itself to you, whether a solution should be made dilute or concentrated to render it more active; certain general rules may be traced. It may be said that a solution passably concentrated is absorbed quicker, penetrates with greater rapidity, produces more considerable effects; while a solution too much diluted produces but feeble effects.

But certain remarks should be made on this rule. If the solution is too concentrated and contains a substance capable of exercising considerable local action, it is clear that in such case absorption, instead of being increased, will become slower. You employ tannin to arrest hemorrhage; it must be prescribed in the solid state; we are obliged thus to have recourse to it; but after having introduced it in the solid form it is necessary to immediately give water to dilute the tannin, because if tannin in the solid state comes in contact with the mucous membrane, so much corrugation is produced that there results almost total impossibility of absorption. It is the same with the ferric salts.

There are other circumstances where the general action is prevented by a too energetic local action. For instance, it is useful, in a certain number of cases, to introduce neutral salts into the economy. Among other diseases, when albuminuria is present conjoined with a state of dyscrasia, you can give with benefit not

only sea salt, but also you can give—and thus aim, at once, at a local treatment and impress the constitution of the patient—mineral waters containing large proportions of neutral salts; for instance, you may give Friederichshall water. I have given it for a long time, knowing that it contains much chloride of sodium and sulphate of soda, to patients affected with albuminuria, through some general morbid state, and I obtained good results. Better still, the waters, which I have called mineral lymphs, because they contain all the salts present in the blood, can be administered, as the waters of St. Nectaire and Royat, which may thus be given to improve the condition of the serum of the blood.

If you give too large a quantity of these waters you will induce purgation. In this event a very small proportion enters the system, although a small quantity enters, for we know, to-day, that even in giving the most energetic purgatives there is always some slight absorption. But the greater the hypersecretion, the less proportion enters by absorption. There are circumstances in which the administration of these substances should not be pushed.

There are also cases when too much dilution injures the effect produced by diffusion. If you desire an example I will compare pure alcoholic liquors with the same when diluted with water. If you say to one to whom you recommend sobriety, "You are gouty, if you take wine in the pure state, it is bad for you," he will reply: "Doctor, I take no more alcohol than you do; you add much water, I take my wine pure, but in the end it amounts to the same." No; when wine or liquors are taken pure, the absorption of the small doses is effected with great rapidity, since all passes and there arrives too great a proportion of alcohol at one time in the blood. On the contrary, where but a fourth part of wine to a glass of water is used, after three or four glasses have been drunk, but one entire glass of pure wine has been taken; and it thus penetrates very slowly, and you have never those violent effects determined by a small quantity of alcohol in an almost pure state, those more

or less durable symptoms of stimulation, which prove so dangerous in heart disease and in gouty affections. You see, consequently, that there are great differences in action with the same doses employed. Again, when you wish to obtain powerful effects from an active substance, such as quinine, you will not give it at long intervals, for there would never be at any one time but a small proportion of quinine in the blood, and one dose would always have sufficient time for its action before the second would arrive; so that there would never be any accumulation of doses, and, consequently, no accumulation of action, for it may be said that the one brings about the other, under conditions which are alike.

These, then, are conditions it is important to be acquainted with. The others which I have spoken to you of are: the degree of division, and the more or less solubility; another, and often artificial condition, is the covering or preparation of remedies. In the pharmacies it is the custom to incorporate active substances with others more or less inert, which are added to aid in their action or obviate too active effect. This disguising medicament, which is often not considered as such, because it is often imagined that true combinations are made, presents more or less obstacle to the activity of the drug, because it opposes its absorption. And in a certain number of cases there is immense difference between the activity of a substance when given pure or in solution, and when given in a divided state, mixed in with an inert substance.

Take, for instance, iodine in the state of a metalloid; it is caustic; it would certainly cause suffering, inflammation, even ulceration, to let fall five centigrams of it into the stomach. But forty centigrams of the iodide of starch, containing four centigrams of iodine, may be introduced; and while five centigrams sufficed to produce the disorders I have mentioned, this dose of iodide of starch has no effect, either local or general. How can this be explained? First, what is known as iodide of starch is not in reality iodide of starch; the iodine is simply incorporated in the interstices offered by the layers of the starch granules,

between which the iodine is present in a state of extreme division; this state of division is the same when introduced into these interstices as when iodine is observed on the internal surface of a bottle in which a few drops of the tincture have been shaken up with more or less force. Under these conditions iodine is blue, and it is on this account that iodide of starch is blue.

The reunion of these two circumstances—disguising in inert matter on one hand, and extreme state of division on the other—cause, then, considerable difference in the mode of action of different remedial agents; so much so, that many preparations which unite both these unfavorable conditions, to wit, first, a very coherent substance, difficult to act on, either by the liquids of the economy or by substances capable of acting through their affinities, such as the alkalies or acids; and again, this substance being disguised in foreign matter, and the entire mass silver-coated, have no action whatever. It will happen to you, from time to time, to administer to patients affected with catarrh of the urinary passages prepared turpentine, considering that in this way you will have all the advantages and none of the inconveniences of the medicament. When these pills are very hard, and well enveloped in a pretty sheet of silver, they pass completely unaltered; they become perpetual pills, as it were.

I have observed this same phenomenon occur with pills of resin of copaiva. I bought from the perfumers resin of copaiva from which they had extracted the essential oil to augment the strength of their various perfumes, and I employed it. I perceived, at first, that I obtained no result, because the pills passed unaltered. I then associated the resin of copaiva with a substance capable of dissolving it, and I obtained good results. You see that the knowledge of this is of practical interest.

I have just shown you that the intensity of the effects produced is not always in proportion to the quantity of the substance employed; that it is necessary that the substance you confide to the digestive organs be of such nature and under such conditions as to be easily absorbed, and with brief delay, so that it may be

retained at one time in sufficiently considerable quantity and in the right proportion to be efficacious.

There are, as I have said, some circumstances entirely paradoxical under which medicaments act least when introduced in most considerable quantity. This would seem favorable to infinitesimal doses. But no: you will see that this circumstance can be explained with facility. Here is an instance. You are all acquainted with the antiplastic action of calomel; you know that in a greater degree than the other mercurials, it affects the salivary glands, and that stomatitis is, alas, too frequently induced, even by small doses. Thus, when it is desired to produce salivation, it is given in divided and very small doses frequently repeated. In this way, if ten or twenty centigrams are administered during the course of the day, stomatitis may be induced in twenty-four hours. It would seem, after that, that it would be very dangerous to introduce large doses of calomel. No: with large doses, no similar effect is produced; it may be that solely cholagogue effects are induced, and no effect at the commencement of the digestive tube; that all the effects, in a word, are felt in the liver. Finally, when enormous doses are employed, no effect at all is produced.

Thus, in India, where physicians employ large doses of calomel to combat a great number of affections (particularly in former times, to-day they have somewhat modified their therapeutics), such as chronic diarrhœas and dysenteries, often four, five and six grams of calomel were administered, which, instead of increasing the diarrhœa, caused its cessation.

Is this homœopathy (*similia similibus curantur*)? No: this simply shows that when the physicians in India gave considerable doses of calomel, there was no possibility even of its partial transformation; the enormous dose surrounded all the substances capable of rendering calomel soluble, and the drug thus passed through the intestines acting as an absorbing substance. This fact is even more evident for oxide of zinc; with small doses, it has nauseating and emetic effects; large doses, absorbing effects. It is excellent to arrest diarrhœa. Why? When you give

little, there is sufficient acid to form lactate and chloride of zinc; when a large quantity is given, a salt so basic results that it is no longer a soluble product, and the zinc passes, producing simply the effects of a chemical absorbent. You see that these facts merit being remembered by you.

CHAPTER XXIX.

Accumulation of Remedial Agents.

Insignificance of small doses. Therapeutic minimum; tolerance and intolerance. State of the organs of absorption; individual conditions; state of the secretions.

GENTLEMEN:

I follow up the enumeration of conditions which cause variations in the actions of medicaments by speaking to you of the insignificant action of small doses. It might be thought that if a substance has an action which might be expressed by 10 at a certain dose, that with a dose ten times smaller its action might be expressed by 1. The facts do not confirm this supposition. There is a minimum dose under which the substance no longer acts, and it passes, it might be said, unperceived. For instance, you may give a milligram of tartar emetic without inducing nausea or vomiting, unless the phenomenon of accumulation of doses, of which we shall shortly speak, is produced. In the same way you can give a gram of castor oil without purging, and that every day in the year. And yet, you will have given during the year 365 grams of castor oil; but there never has been enough at any time in the organism to produce sensible effects.

This fact, verified with facility for castor oil, exists also for other medicaments, of which the action is less visible. Efficacious doses are needed, as I have written long ago in "Trousseau's Therapeutics;" under these doses no effects are produced. Another reservation to make in regard to the proportion of doses is this: not only the effects may not be in proportion to the dose, but it will be observed that when the dose is gradually increased there is a change in the effects produced. I cite as an instance, opium or morphine. With small doses there are excitation and drunken-

ness, stimulation; so much so that the eastern nations seek this stimulation and often go to combat after having taken a small dose of opium. But a relatively feeble dose of opium is required to produce a stimulation of the circulation analogous to that produced by alcohol. On the contrary, with a somewhat more elevated dose, you will have those phenomena of cerebral congestion which render opium the most powerful of hypnotics and of stupefying agents affecting the sensory nervous system. What happens for opium in more or less elevated doses, and on the other hand, in feeble doses, of which I have spoken, happens also for digitalis, which produces entirely different effects when the dose is moderate from those observed when the doses are excessive and beyond the usual quantity. With moderate doses the pulse becomes slower, each pulsation augmenting in force, the peripheral circulation being accomplished with the more activity that the cardiac revolutions are less numerous; but on the contrary, the tension augments when the dose has been further augmented. The dose may not be too large when a single dose is introduced, but on account of the accumulation apt to occur, toxical phenomena will be observed. The pulse is at first accelerated, and while with moderate doses it underwent a change favorable for the circulation, becoming slower, with over doses the circulation becomes embarrassed, the pulse becomes irregular and insensible, in short, toxical phenomena result. You have at the same time all the phenomena of intolerance well known in the history of digitalis. Consequently, as you see, not only the physiological effects are not always increased by increase of the dose, but often the action is modified.

We have just seen what influence the dose has on the therapeutic power of a drug, with all the reservations necessary as regards the comprehension of facts in appearance paradoxical. I have spoken to you, also, of the influence of all the physical and chemical circumstances existing in remedies, and which may modify their conditions of solubility.

It is necessary, now, to consider what influences, on the part of the subject who ingests medicaments, modify their activity.

There exist, on the part of the patient, conditions sometimes eminently favorable, in other cases very unfavorable. As to the action of remedial agents, it is necessary to be acquainted with them and have their effects in consideration in prescribing, for you will be obliged, according to circumstances, to take certain precautions in order to cause the remedies to be accepted by the economy and to assure their effects. I will pass in review, one after the other, the state of the organs and the functions—activity, inertia, the natural or acquired effect of impressions on the patient, the state as regards tolerance and intolerance.

I will say a few words on age, sex and race, for there are considerable differences observed in the manner races are affected by medicaments, and this is not the least interesting part of our subject. In the first place, as regards the organs of absorption, we find here considerations of vascular tension, which are of extreme importance, and you will see that in ancient practice the importance of these conditions was understood when science was less advanced. Sometimes tension is active; at other periods tension is passive.

Is there any necessity of defining these terms? Yes; for considerable confusion exists, and generally two phenomena, distinct from each other, and often opposed one to the other, are confounded.

Passive tension is represented when one finger is compressed between two others, since by this process all the blood in the finger is forced toward its extremity, and maintained there; this kind of tension is confounded with active tension, which consists in this: not only is there considerable force of propulsion on the part of the central organ of circulation, but there is considerable energy of contractile power in the entire vascular system. With these two conditions, great force of propulsion with considerable contraction, you will have what is termed elevated tension. It is this state alone to which attention is generally attracted; but, nevertheless, there are cases where the tension is purely passive, resulting from a diminution in the contractility of the vessels. It is passive from this point of view,

but is, nevertheless, the result of some change taking place since the vessels have lost their tonicity. This passive tension is augmented under the influence of the absorption of a large quantity of liquid, or when such is present in the blood. This is what happens in true aqueous plethora, or when the blood is very abundant. We can have this state of veritable plethora under peculiar and various conditions, as has been pointed out by Magendie; thus a sort of conditional and necessary plethora exists momentarily after a repast, where a large quantity of aliments and liquids have been ingested; and you will observe considerable variations as regards this state of aqueous plethora, according as the subject has or has not just been ingesting fluids. This is so true, that the day after a general or local bleeding, after having the day previously noted the absence of any murmur in the vessels of the neck, it will be found that when the patient has taken liquids, introducing water to replace the blood lost, a fine bruit, due to the anæmic state and the hydræmic condition of the blood, can be heard; a double murmur, the true *bruit du diable.**

You can see, then, that when a large quantity of blood has been taken from the system there is no murmur; this murmur is perceived only after the loss has been repaired by the ingestion of liquids. There are also states of localized passive tension which result from mechanical obstacles being opposed to the venous circulation, as in cases where the blood in the veins mounting almost perpendicularly, there is more or less stasis through compression of an important vein. In this case of venous stasis there is difficulty in the introduction of medicaments by the cutaneous surfaces. There are also cases in which a state of active hyperæmia, a veritable state of more or less intense phlogosis, sometimes of plastic variety, opposes obstacles to absorption. Every body knows that when inflammation exists the inflamed surface is little apt to absorb the active substance deposited on its surface.

* The souffle found in the vessels of the neck in anæmia is called in France "bruit du diable," from the supposed resemblance between it and the sound produced by a child's plaything called "le diable."

There are a variety of practical applications to be made of this fact—that absorption is diminished under the influence of a state of exaggerated passive tension. This should show you that when you wish to have as rapid absorption as possible, the medicaments should not be administered when the stomach is full, or when there is plethora, determined by a large meal.

There is another well known circumstance: that is, when it is desired to prevent absorption, an artificial obstacle to the return of the venous blood may be created. When a person has been stung or bitten by an animal, it is, of course, of benefit to cauterize, but a caustic substance is not always at hand, while compression can be made with great facility while waiting until a caustic can be procured, to afford the subject protection against ulterior accidents. This will suggest to you that when you wish to render a cutaneous surface prepared by a blister more capable of absorption, it must be so arranged that this blistered surface be not in an inflammatory state at the time of the application. Thus, it has been observed that when a vesicated surface is very much inflamed it absorbs very little, and that even large doses of morphine have no effect on the general system. And there is another sequence to be drawn from these considerations: when you have to deal with a plethoric subject presenting a state of hyperæmia of various organs—a large liver, such as gouty individuals or those who live somewhat too highly—it is necessary to commence treatment by depletion. If you do not commence by emptying, as it were, your patient, you will obtain almost nothing from medicaments. Thus, it is very often necessary to give an emeto-cathartic to a patient in rheumatism, whom yon may wish to submit to the influence either of sulphate of quinine, or of any other substance which must be absorbed. You will do the same when, in the course of a disease of the heart, you wish to employ digitalis or the diuretics.

When you have, then, to deal with men overstocked with blood, commence, I repeat, by depletion. It is only when you have, as it were, made room, that you can with utility commence

to prescribe digitalis. It is the same with the sudorifics: they do not act in subjects whose systems contain too large a proportion of liquid materials.

When you make use of the antiplastics, you should use mercury for its purgative effects, before attempting to obtain the other virtues it possesses. Suppose you have to deal with a malady such as psoriasis. If you wish to give mercury it will be necessary first to purge the patient several times. And with even greater reason when it is wished to induce the resolution of morbid swellings, etc.; it is clear that in such a case it is necessary to commence by removing from the tissues all the materials which usually oppose obstacles to the resolvent action of iodide of potassium, and of like medicaments.

In cases where the active tension is augmented, almost the opposite rules to those of which we have spoken would be applied. If you have very marked active tension, and at the same time an empty state of the meshes of cellular tissue, then you have the circumstances most favorable to absorption, and consequently to remedial action. It is the exact opposite of the state we have just been considering. This is so true, the knowledge of these facts is so ancient, that among all people you will find in vogue practices which consist in diminishing this active tension, diminishing this vascular rigidity, and attempting to bring about the condition of passive tension of which I have just shown you the inconveniences.

For instance, when a negro in the Antilles or Senegal is bitten by a venomous serpent, he is submitted, as a matter of course, to alcohol in very large doses, while at the same time sudorifics are given. He is made drunk, and left dead drunk, when it is wished to prevent him from dying from the action of a poison such as that of the crotalus or trigonocephalus. Why this practice? Because during this powerful action of alcohol there is, as you know, universal congestive tension. These individuals have all the tissues congested, and while in the state of general hyperæmia they do not absorb, and consequently they escape the mortal, or very noxious effects of the poison; for the poison, just

as for the medicaments, what makes the activity is the quantity at any one moment present in the economy, and which may thus act all at once, either on the nervous system or on the heart. You see, then, that there are certain popular practices which show us how, with the aid of instinct alone, the existence of certain physiological conditions have been divined which science has not discovered until later.

There are also some chemical conditions of the cavities in which absorption should take place, which cause variations in the activity, and hence in the physiological and remedial effects of medicaments.

We know that the presence of acids, of alkalies, of albuminoid substances, and of fatty matters, is, if not indispensable, at least of use in aiding the absorption of a large number of medicaments of themselves rather difficult of dissolution. It suffices to know this general law—the necessity of the presence of modifying substances—to understand that, according as they are in abundance, in small proportion, or not at all present, there will be facility or difficulty of absorption, or no absorption at all. Thus the acidity of the stomach will favor the introduction of all the substances which are in need of acid to penetrate into the economy; such as the metals and very insoluble acid salts. And thus, again, the opposite condition will prevent absorption. Alkalinity of the intestine is favorable to the absorption of a certain number of substances, and in particular, of arsenious acid, as also of salts having an alkaline or an earthy base, and which have acids rendering them insoluble. Thus the tartrates and the oxalates of lime, of potash and soda, are little soluble when they are acid, but if they are easily soluble then they are alkaline and basic. Consequently, they can penetrate with more facility when the amount of alkali which they meet with in the intestine is more considerable.

We may say the same of alkaline chlorides, albuminoid principles and fatty matters, which aid in the introduction of certain metallic substances, soluble in albuminoid principles; or of phosphorus and sulphur solution in fatty matters.

When food too much salted is taken at the same time with a large dose of calomel, marked poisoning may result by the formation of a very poisonous double chloride. The chloride of sodium may also have accumulated (from articles of food containing a too large proportion of salt), before the introduction of the medicament. It is clear that you will not obtain the same effects among patients entirely deprived of salt, as during the siege of a city. It is the same for albuminoid principles; they are first favorable to the dissolution, then to the absorption, of substances rendered soluble by them.

Some conditions peculiar to individuals are without great importance—the rapidity of the circulation, the speed with which the substances penetrate into the tissues. But there are other conditions of real and great importance. Such is the rapidity of molecular change; this has great influence upon the physiological action of substances which are about to take part in tissue formation, as the renovation is, on this account, made with more or less rapidity. There is also the rapidity with which the substances are destroyed; for the important point is, not how large a quantity has been introduced, or which has been circulating in the blood, but the quantity which is present in a state to act at any one moment on the system. It can be easily understood that if a substance is introduced, even in large quantity, and is destroyed with extreme facility, there is never sufficient present to produce remedial or toxic effects.

Another condition of weight, as modifying the intensity of physiological action, is the state of the secretions.

If the salivary, biliary, and in particular, the urinary secretions are very active, when, consequently, there is great rapidity of excretion, there will be great difficulty in producing any considerable remedial effect, and in order to obtain such it will be necessary to prescribe very large doses. If this condition is excellent in a certain number of cases where it is desired to eliminate a poison, it is unfortunate in others, where it is desirable to produce remedial effects. If the secretions are in a languid state or completely dried up, a parched mouth, with anuria or

oliguria, under these conditions even small doses of active substances will produce considerable effect, and you must be guarded in administering remedies. When, then, you wish to introduce medicaments of great energy, particularly in subjects requiring more circumspection than others, such as gouty individuals, for instance, it will be prudent to inform yourself if they pass much urine or but little. If the kidneys secrete abundantly you may give colchicum and every kind of active substance, without any fear of going beyond the usual therapeutic limits; if, on the contrary, the urine is scanty, if but five hundred or six hundred grams are excreted in twenty-four hours, be on your guard; give but feeble doses, because accumulation might take place, and you would go much beyond the therapeutic dose. It is in such cases that accidents, often formidable, are induced through the influence of moderate doses. You see that it is indispensable to take into account these conditions of elimination and secretion. It is through such influences that quite a number of substances which we employ are sometimes tolerated and sometimes produce toxic effects, as sulphate of quinine, which, if it accumulates, may be followed by such results as troubles of vision, noises in the ears, and deafness, which may persist for months and often for years, and which may become incurable; yet, in other cases, and even with large doses, this same drug may determine none of these symptoms, or, at least, not sufficiently to be disagreeable. You will have but a slight quinic intoxication, and no dangerous symptoms. The difference lies in the fact that in the first case the secretions were not well performed, the urine was scanty, while in the second this secretion was abundant.

It is the same for salicylic acid, which sometimes leads to grave accidents, death even, and at other times is perfectly tolerated. This is because in the former case it came in contact with a very irritable kidney, and brought on oliguria and even anuria, while on the other hand, in certain subjects, it but renders the urinary secretion more active. The same is the case with arsenic. I have shown you that the intensity of the action of arsenic should not be judged from the dose alone, but also from the

quantity which might be retained. If it is eliminated, it is nothing; if on the contrary it is retained, even when but a small quantity enters, the result may be very grave. In pathology you will find similar facts: How does it happen that with advanced lesions of the kidney there are patients living who appear to be in good health, and have never any symptoms of uræmia? This happens because they pass a large quantity of urine. But it must not be thought that they pass one or two litres (quarts) of urine per diem; they pass three, six or eight litres in the twenty-four hours. I have even now, in my service, a patient presenting this phenomenon, and who, on account of the large quantity of urine passed in the twenty-four hours, has never had a symptom of uraemia. Suppose the opposite condition; the filter is more or less clogged up; you will then see appear all the evidences of uræmia, with the well known symptoms which it presents. To sum up, the union of these two conditions—on one hand facile absorption, and difficult excretion, on the other difficult absorption and rapid excretion—induce enentirely opposite phenomena; in the first case there will be considerable augmentation of all the effects, physiological, and sometimes toxic, produced by the substance introduced, while in the other case a compensation is established between what enters and what is excreted, between the exportations and the importations; there are no symptoms produced and no toxic effect.

I will now speak to you of a question exceedingly interesting from many points of view; in the first place, by the symptoms produced, and again, from its practical applications: I refer to the *accumulation* of medicaments. This accumulation comprises two series of facts which differ less than is generally supposed; accumulation of action, and accumulation of doses. We will first speak of the accumulation of doses; it is the part most easily understood, and which also causes the most dangerous results. This accumulation of doses consists in this: it is an aggregation or collection in the primæ viæ of the substances introduced, and which, instead of traversing the membranes open to them, remain

there, without being dissolved, without penetrating and without acting. There may be two results; sometimes the substances form a sort of metallic mass (gisement metallique), as I have called it on another occasion, and this mass remains there without undergoing any new modification. In other cases, on the contrary, it is but a species of reserve, as we will shortly show, which is taken up later to penetrate into the circulation. There are two conditions under which this accumulation takes place. In the first, the accumulation is due to a deficient absorption. The substance is soluble as usual, it is sometimes even markedly soluble; but what is wanting is the absorbing power of the surface with which it is in contact, and this defect is met under very diverse circumstances.

What will render this subject most clear is what happens in cholera. In this disease you give remedies of decided activity, and they produce absolutely no effect; it is thought that they are inert, that it is of no use to have recourse to them. Nothing of the kind. This effect is due to another circumstance, as you will see; it happens because the medicaments are not dissolved, and in other cases, because, though introduced in a state of solution, they come in contact with a mucous membrane unfit for absorption, because it secretes too much. For you know that there is an inverse relation between absorption and secretion. If there is enormous hypercrinesis, there is no absorption.

You may also meet with this defect of absorption produced by dessicating substances. Thus, for instance, after the introduction of large doses of opium and belladonna into the digestive tube, you may observe that certain substances can be introduced with impunity, for they are no longer absorbed. The mucous membrane is not only narcotized, it is also in a dry state.

There are other cases where, the absorbing faculty being intact, the substance introduced is covered up in the midst of inert matter, hard, and not capable of dissolution. Of course in such cases there is no effect, no absorption possible, for it can be effected solely on dissolved substances; with, however, the exceptions I have already mentioned, that there is sometimes absorption of

solid substances by a mechanical penetration, analogous to that of a blade of grass traversing the polyporus lucidus.

We have on record cases where pills, of careless manufacture, resisted the diluting and dissolving action of water and of the various liquids contained in the primæ viæ; I have cited to you the case of the perpetual pills, as those of the resins; I will cite here pills of more soluble substances, as of the extract of opium, but made for a considerable period. The case has been reported of a man who succumbed to tetanus, without having presented any effect from the opium, which was given in considerable doses; but at the post-mortem a collection of opium pills was found in the intestine, all intact. This same fact has been noted in cholera. The conclusion to be drawn from these facts is that opium should always be given in a soluble form.

There are also substances naturally very insoluble, such as the metals, certain metallic salts, certain chlorides (of the metalloids), certain acid salts, even those acidified by tartaric acid, which may also be accumulated by the same process in the primæ viæ, through their more or less considerable difficulty of absorption. I observed that through whatever mechanism this accumulation took place, there are two cases to distinguish. Sometimes the substances which have been introduced remain indefinitely in the condition of foreign bodies; again they simply form reserves, which will be later taken up and become active.

As an example of the first fact, I will cite the curious bezoars (concretions) of magnesia, found so frequently in the intestines of horses. Such concretions were also found in the cæcum of an aged Englishman, who took, every morning, a spoonful of magnesia; there was not always sufficient chlorhydric, or lactic, or carbonic acid present to dissolve it, consequently the magnesia accumulated in the part of the intestine where the greatest mechanical difficulty to its elimination existed. This bezoar stone was as large as the fist. But there is an accident which may happen; that is, the substance may be taken up later; this is what happens in cholera.

These same pills of opium, which have been found intact and

not altered, have in the end been attacked, and here is what is observed: In the height of the attack large doses of opium were given, and without effect, then the symptoms change spontaneously; that is, reaction commences, and with it new conditions of the mucous membrane of the digestive organs; the hypercrinesis is replaced by a somewhat dry state. At this moment absorption takes place, the pills are, at least in great part, dissolved, and all of a sudden symptoms of opium poisoning supervene. This is what has been observed also for pills of nux vomica, of strychnine, of phosphide of zinc even. After having obtained no result, acute phenomena of poisoning suddenly startle the physician.

CHAPTER XXX.

Prevention of Accumulation.

Means o avoid accumuiation of doses; administration in pill form con emned. Accumulation of action different from accumulation of doses; causes and variations of accumulation of action.

GENTLEMEN.

To avoid accumulation of doses, the best means is not to employ medicaments in the solid state. Pills, particularly when well prepared, and enveloped in metallic covering, are bad preparations. They render service assuredly, for it is the most commodious means of administering medicaments, but it is also the least secure method, and when you desire the assured and prompt action of a remedy, you must not employ pills.

There is reason, also, to desire the pills made in a certain way; a little glycerine favors the dilution of the substance and its absorption. But oftenest it will be necessary, when you have to deal with serious or grave affections, to have recourse not only to soluble substances, but also to substances already dissolved, given in the form of syrups and potions, and even in the state of very dilute solutions, so as to be sure of giving a dose equivalent to the effects you wish to produce. These very dilute solutions render great service; it is through them that a certain known quantity of a substance can be added to a potion. Syrups also are useful.

You know that Trousseau, after having seen how much danger there was in giving strychnine in pill form to young patients in chorea, finished by prescribing a syrup called after him, and which contains sulphate of strychnia. It is certain of producing effects, which vary according to the quantity given, and according to the state of the subject as regards absorption, but

effects always in relation with the dose; it gives, consequently, excellent results.

It is desirable, also, to administer well defined substances, and which are sufficiently soluble with the aid of certain adjuvants. When you employ these substances the modifying agent should always be added to the preparation you make use of. I will explain: take, for instance, salicylic acid, which is not at all soluble; it is necessary to give bicarbonate of soda at the same time with it. I take this example, not because I recommend salicylic acid, but because this acid being a dangerous substance, on account of its topical action, I wish, at least, to spare you the greatest of errors, and advise you to employ it in the state of a salt.

These recommendations which I make concerning this acid, I would repeat with even more reason in reference to sulphate of quinine, which is soluble, but in small proportion. The acid sulphate is comparatively soluble; it is, then, preferable to attempt the transformation of the neutral sulphate into the acid sulphate. So that whenever you prescribe sulphate of quinine for your patients, it will be desirable to order it in solution, and you will be often able to induce even women to take this bitter sulphate of quinine, if you will explain to them the advantages of taking it in the liquid state. If you administer sulphate of quinine in the solid state, and in pretty large doses, as is often required in intermittent fever when intense, you will expose yourself, when you have given a mass of at least twenty-five or fifty centigrams in the solid crystalline state, to produce phenomena of gastric irritation, perhaps quite intense, and when these phenomena are repeated, to induce a veritable artificial gastritis, which might be said to be toxic, and which lasts after the administration of the drug has been stopped. If, on the contrary, you arrange it so that the dissolution of the sulphate of quinine be aided by the ingestion just after the sulphate of an acid solution, lemonade with citric acid, for instance, in such case you will be less likely to have these inconveniences.

But you will do better if you first dissolve the sulphate of quinine in lime juice; you can, with one teaspoonful, obtain

the dissolution of twenty-five centigrams of the salt, and I can assure you that this solution is not at all disagreeable for the majority of patients, and that it proves of double benefit, inasmuch as you avoid the disagreeable local effects, and are assured of the action of the sulphate of quinine, not only because all is introduced, but because it is almost immediately absorbed through this state of great solubility. Here, consequently, is an occasion where you should not fail to accompany the active substance with its modifying agent. There are, nevertheless, circumstances which render it impossible to have the substance in such a state of solution. You are obliged to use substances which become soluble after a length of time, and which, consequently, have to be introduced into the primæ viæ just as we receive them from the druggist. Take, for instance, calomel; you cannot dissolve it. It would be soluble in the chlorides, but it would be no longer calomel, and you wish to have it with its own peculiar properties.

Here is the artifice you will employ. It is an English physician, Law, who has shown us how the effects of calomel on the general system may be assured. Here is his manner of procedure, and it is one very generally adopted at present. The doses are to be very small; for instance, it may be but one centigram at a time in sugar of milk, to augment the size and aid in the division of the dose; five centigrams is thus given in twenty-four hours, in five or ten doses. Under this form calomel, notwithstanding the insignificance of the dose, produces considerable effects, and this is why: introduced in very small doses, it finds in the primæ viæ the necessary modifying agents to bring about its dissolution, not chloride of sodium (it is, in fact, very fortunate that there is not much of this salt present, it would make a double chloride), but it comes in contact with mucus, which dissolves it. It penetrates, with the albuminoid principles, into the blood: then a new dose arrives, very small, like the preceding; it is completely dissolved, passes into the circulation, and goes to augment the dose already present in the blood. And so on, the solution being thus effected for each of the doses.

When calomel has thus been given, very decided results are obtained from small doses, so much so that from one day to the next, sometimes, symptoms of salivation appear, and in the space of two days a marked sialorrhœa occurs, and after three days phenomena of mercurial stomatitis may ensue. If, on the contrary, the same quantity had been given at one dose, and if it had encountered difficulties in the way of dissolution, it would have induced symptoms of considerable local irritation, and, being taken up by the hepatic gland, it would have been rejected from the economy. There would have been symptoms of irritation of the secreting part of the liver, purgative or cholagogue effects on the intestine, but no general effects. This method has given very good results, and is generally employed when it is desired to produce antiplastic or constitutional action.

I come, now, to another aspect of the question concerning the accumulation of action. We have just seen what accumulation of doses signifies; we will now consider what is accumulation of action.

It is observed that in administering a medicament several days, one after the other, giving each day the same dose, the phenomena due to the action of this medicament become more and more intense.

This may occur even when it be known for certain that all given each day was absorbed the day it was ingested, produced its effects, and had sufficient time for elimination, when elimination could have been made in this space of time. This phenomenon of increase in the intensity of remedial action—the dose remaining the same—should not be confounded with the pseudo-accumulation of action which results from accumulation of doses, and in certain cases from a change in the pharmaceutic preparation. For it is well that you be warned that it suffices often to change the pharmaceutic preparation, in order to have symptoms more or less grave supervene, even employing the same dose as on the preceding day. This is another point which experience teaches us, and on which Trousseau has insisted. He had remarked that when he gave strychnine or nux vomica

in pills, and when at certain periods he was obliged to augment the dose and preparation, to obtain very powerful physiological effects, there supervened, the following day, all of a sudden, symptoms, of more or less gravity, of poisoning by strychnine. He finished by noticing that it was not alone an accumulation of doses which produced this phenomenon, but that also the change in the pharmaceutical substance had its part. That is to say, that after a certain time drugs become altered in the pharmacies, and particularly extracts, when they have been prepared for a time. This is why, after having administered a dose already considerable, of nux vomica, another extract recently prepared, and consequently of great energy, being given in the same dose, it is possible that toxic symptoms will be produced. You see that this is a phenomenon which differs from accumulation of action.

I give you another fact: when a substance like strychnine is employed in the state of syrup of the sulphate of strychnine, when it is given in fractional doses, and when the same dose is repeated every day; here there is no possibility of accumulation of doses, since all is instantly absorbed, and there is not either any change in the substance, sulphate of strychnine being always the same; yet, nevertheless, this progressive increase in the intensity of its action is observed! And what I here say to you for strychnine is true for a great number of substances. How can this phenomenon be explained? It would seem that the process is as if the intervals between the successive doses administered of the active substance were sufficiently short, so that a portion of the action of the first doses persists in the system at the time the following dose is administered, and so on for the following doses. Suppose, in this particular case, that the effect of the first dose be represented by 20, and that of this effect represented by 20 there persists the half, that is, 10. And that the third day there subsists 5, the fourth of the primary effect. You can easily understand what will happen.

When you give the same dose, producing an action represented by 20, on three successive days, if there subsists 10 of the prim-

ary effect, you will have the second day an effect represented by 30, and on the third by 35. All kinds of figures might be taken to represent this phenomenon; those which I have chosen are simple, and render account of the fact.

We will now attempt to explain the mechanism through which is brought about this persistence of action of a substance, administered always at the same dose, but which, nevertheless, induces effects more and more intense, effects constituting what is called accumulation of action. It is to be noted that these phenomena of accumulation are observed, generally, with pretty large doses, or else moderate doses when given at short intervals, and with substances which pass slowly through the organism. You can readily understand that there will be no accumulation with feeble doses, for they are destroyed and eliminated with facility, nor with substances which pass easily through the economy, and which act, for instance, solely on the globules. You know that these substances are generally eliminated with great rapidity, as are the gases themselves; ether, chloroform, ammonia, in fine, all the substances which act principally on the blood, are eliminated with celerity, and accumulation is difficult. On the contrary, the substances which sojourn more or less in the system, which penetrate into the parenchyma, which at last are incorporated with the immediate principles, or with the cellular parietes; or, again, which take part in tissue formation, such substances are the ones which show themselves particularly favorable for the production of what is called accumulation of action.

Where do you find the substances, in relation to which this accumulation has been cited? I have spoken to you of strychnine, which acts on the elements of the medulla, penetrating and sojourning in them. You will find the same true for digitalis, and it is one of the best examples. We will return to this latter drug, for it presents a peculiarity not observed for other substances. You will observe the same phenomenon with arsenic, mercury, phosphorus, and lead. Lead furnishes perhaps the most favorable example to demonstrate

what influence the mode of penetration of a substance into the system has on the accumulation of action. Thus, very small doses of lead, but repeated every day, finish, in the end, by determining very grave symptoms, since different forms of paralysis, and death even, may result. These are the substances, and they are precisely those which adhere most, as it were, to the organism. Now, how should their effects be understood? In what manner do they proceed in order to augment progressively, the doses remaining the same, the intensity of their effects? It may be supposed that what occurs in the living organism, through the influence of modifying agents which we introduce for a remedial purpose, bears some resemblance to what occurs in a storm. You have seen great poplars, bent under the force of the wind, return toward the erect position, and again incline under the force of the blast to an angle of 45°, and even less, with the horizon. With each blast the tree is bent lower than before, and in greater proportion. It may be supposed that something analogous takes place when medicaments commence to produce their effects; first, a deviation in the function of the cell takes place, there is increase or lowering in functional activity, then a new dose arriving, increases this deviation. This manner of regarding the subject is admissible, but is somewhat too hypothetical, and does not repose on facts proven with sufficient certainty.

Another supposition, which it appears more easy to admit, is, that a certain fraction of the active substance remains permanent in the interior of the tissue it modifies. You can well understand, to take up again our example, that if out of twenty parts of the active substance (say digitalis or digitaline) but ten parts are eliminated or destroyed each day, if ten parts remain in the histological elements of the bulb, at the point of origin of the sensory nerves, when the next day twenty new parts of digitaline are added, there will be thirty parts situated in the bulb, to modify the functional activity of the heart. It would seem that, in reality, it is thus events occur. So that there would be no great difference, in taking this view of the subject, between accumulation of doses and accumulation of action; and

it might be said, the accumulation of doses is the accumulation of medicaments in the primæ viæ; accumulation of action is the accumulation of medicaments in the organs where they accomplish their destiny. And thus all is explained by this sojourn, more or less prolonged, in the organ which the active substance chooses, in its organ of election.

This explanation is sufficient in the great proportion of cases, but it is insufficient as regards digitalis. For this remedy exhibits a very curious peculiarity, well known for a long period, but which has not yet been sufficiently studied in all its details, and to which recent works have again called the attention of practitioners. I would speak of the augmentation of the phenomena of digitalism, observed when its administration has been arrested. Thus this is frequently observed when the alcoholic tincture is given in the dose of twenty or thirty drops a day, or the infusion in the dose of fifty centigrams, or the powder of the leaves of digitalis. Some remarkable phenomena are thus obtained and have provoked much discussion at various times, but which are well explained to-day; the progressive slowing up of the beating of the heart and the augmentation in strength of the cardiac propulsion. After five or six days the pulse will fall to 80, from 130 or 150, which it was at first. At this moment the prudent practitioner arrests the use of the drug, and leaves the digitalis to accomplish what remains—that is, to reduce the pulse to 60 beats. And it happens in a great number of cases that the slowing up of the pulse continues, not only for twenty-four hours, but also for the four or five days succeeding. So that the pulse, which he left at 80 when ceasing to employ the remedy, finishes by falling to 40 beats. And this slowing up may last for a longer period, even, than that I have mentioned. In several observations a much longer delay has been cited, and my friend, M. Quevenne, has shown in his experiments that this peculiar retardation which follows the administration of digitalis might last ten or even fifteen days. Even this term may be exceeded. I had lately in my service at Beaujon a man affected with an organic disease of the heart, and to whom

digitalis had been given in proper doses to render the beating of the heart slower. This progressive retardation lasted twelve or fifteen days at 54 to 45 pulsations. He left the hospital to see a public celebration, saying that he would probably never see another fête. Durozier, has cited a case where this slowing up lasted twenty-five days.

I may say that for these facts the explanation given just now is insufficient. We contented ourselves with saying that a small quantity of the medicament remained in its organ of election, in the medulla oblongata, or in the brain, if you wish, and that this portion which thus remains receives each day additions from the new doses introduced. But in this case the medicament has been suppressed; another explanation must hence be sought. It is probably the following: a substance does not immediately penetrate into the organs it modifies; during a certain period it is in the circulation, or is in reserve in the interstices of the cellular tissue, or in the initial lacunæ of the lymphatic network of the organs where it is undergoing elimination, but whence it is eliminated somewhat slowly.

It must be admitted that there is evidently an accumulation of doses in the circulatory system, and in all the organs, which may serve as a reserve for the active substance. You see that the more we study the phenomenon, the more certain we become that accumulation of action and accumulation of doses have a very close relation to each other. In short, it may be said: accumulation of doses is the storing-up in the primæ viæ; accumulation of action is the storing-up in the organ on which the remedial agent exercises its action.

Now, what are the circumstances modifying this accumulation of action? One of the principal circumstances, and which I have already placed in relief, is the rapidity with which elimination is produced. When I spoke to you of arsenic, I said: It is possible that even strong doses be eliminated, but before this occurs they have already produced effects which, by repetition, determine dangerous phenomena as regards the digestive organs, and which may finish by destroying the sources of life. This same elimina-

tion, slow or more rapid, intervenes again in this instance, since digitalis cannot maintain its effects, unless it is held in reserve in the tissues. It is not then eliminated gradually and completely, during the period it penetrates. In effect, it is one of the substances most difficult of elimination. It would seem to be eliminated but by few organs, and I have reason to think that it is discharged particularly by the liver. What is well known is that it does not seem to be eliminated by the kidneys (which is, nevertheless, the ordinary route for most substances), and this is so true that the taste of digitalis has never been found in the urine.

Thus M. Quevenne, who carried scientific devotion to the most extreme limits, said that, notwithstanding the large doses he employed in his experiments, he had never been able to find in the urine a bitterness recalling that of digitalis. You know that it is of such bitterness, that the smallest quantity present in a liquid suffices to give it a flavor which will leave no doubt of its presence. This is so true that when you take an infinitesimal quantity of amorphous powder of digitalis, like that of Homolle, and place it on the end of the tongue, it will give you a taste of terrible bitterness. And, nevertheless, it is almost insoluble in water. You can then understand that if, being insoluble, it gives so bitter a flavor, its power to indicate its presence must be excessive. It is to this prolonged sojourn that digitalis owes its power of influencing the organs apt to be influenced by it, even when its administration has been stopped. There is always possibility of accumulation of action for a certain number of bodies, for quinine in particular. It suffices that the doses be administered at somewhat short intervals, in order that a sufficiently considerable quantity of the active principle be always present in the economy, to end by saturating, as it were, the system, and thus producing phenomena of accumulation. This is what takes place for quinine, for morphine and for atropine.

I will speak to you of other circumstances which modify the intensity of phenomena due to accumulation of action.

This accumulation is limited by the destruction of the substance, and by the greater or less rapidity with which denutrition and disassimilation are effected. This is so true, that with substances essentially *cumulative*, as English physicians express it, especially metallic substances, something may be done in opposition to this accumulation in the nervous system by administering iodide of potassium.

Melsens, who first demonstrated this influence of iodide of potassium received the "grand prize" for new observations regarding this subject. It suffices, he affirms, that while individuals are exposed to emanations from lead, iodide of potassium be concurrently administered, to prevent there being at any time sufficient saturation of the nervous centres by lead for these individuals to present phenomena of paralysis. This is a great service rendered to humanity, and the prize was justly decreed.

There is another circumstance which also limits accumulation of action, that is, the force of habit. Without doubt, we observe substances accumulate in the nervous system, and these determine effects more and more considerable, finally becoming dangerous; but there is also in our economy a disposition which may be expressed by the term "force of habit," by virtue of which we resist more and more the action of remedial or toxic agents, just as we resist in like manner many exterior conditions which might injure us.

We will attempt to understand in what this force of habit consists, and how it may be interpreted. It may be expressed in this proposition: progressive diminution in the action of modifying substances with which we are in contact. This progressive diminution may be due, either to the lessening of our susceptibility as regards the drug, or that we react with ever increasing vigor against the action of the substance. This gradual enfeeblement of the action exercised by modifying agents on our economy is not in equal proportion for all. There have been such differences noted that observers have found themselves obliged to seek some explanation for them.

My colleague, Bouchardat, has affirmed that these differences

are due to the following facts: we find on the one hand substances which in sufficiently large doses are poisonous for higher organisms only; on the other hand, substances poisonous for all living organisms no matter at what degree of the scale they may be placed. Now, he affirms, poisons which are poisons for all forms of organic life are substances to which no one becomes accustomed; on the other hand, individuals may become accustomed to substances which are poisonous only for the higher organisms.

I have no wish to refute this manner of explaining away the difficulty; I believe, even, that it is sufficiently accurate. But it leads to this conclusion: No one can become accustomed to poisons noxious for all living beings, because no one can become habituated to substances which exercise their poisonous action on the faculties which are possessed in common by all, such as nutrition and the generative functions. On the contrary, habit may give impunity when these substances attack faculties added to these and possessed alone by the superior animals, such as the nervous system, with its various attributes, and the faculties of an elevated order, which they possess, and which do not form an essential part of all living beings. I contend that if the proposition advanced by Bouchardat is true, it should be said that the substances to which habit gives no impunity are those which are poisonous for those functions which may be called elementary for all living beings; but in such case substances which act as violent poisons on inferior organisms should not be tolerated by animals placed higher in the scale, as has been observed. You are all familiar with the powder of the *pyrethrum roseum.* This is a poison of extreme energy for insects, but for the superior animals it is almost inert; it can hardly, even, be considered as disagreeable. Other plants, such as tansy, are disagreeable; they do not please our sense of smell, but they do not poison us.

You see, then, that there are substances poisonous for inferior beings and which are without effect on superior beings, even when taken under analogous conditions. This peculiarity prevents me from admitting without reserve the correctness of the

proposition I have just indicated. To mention it in passing, this possibility of substances inoffensive for the superior organism producing toxic effects on the inferior, gives hope that some day those inferior organisms which, according to Pasteur, are the fundamental causes of most contagious diseases, may be combated by means which would not be dangerous for the superior organism carrying in the system these contagious principles.

I think that a distinction of more practical value might be made between mineral poisons on the one hand, and organic poisons on the other.

Habit does not give impunity against the mineral poisons; no person exposed to them can escape poisoning by arsenic, or by lead. There are individuals who resist, more or less, but accidents are inevitably produced in the end. On the contrary, organic substances which are destructible are principles toward which we acquire impunity through force of habit. If there is no Mithridates for arsenic or lead, there is for opium, for belladonna, and particularly for tobacco.

Such, then, is the true distinction to be made; mineral substances on the one hand, and organic substances on the other. Yet, exceptions must be noted, for there are organic substances against which habit gives no impunity. There are experiments made by Claude Bernard, which demonstrate that if a certain dose of curare is given to an animal, it will be noticed that the effects last so many minutes; if the next day the experiment is repeated with the same dose, and the same substance, exactly the same results, having the same course, and lasting the same length of time, are obtained. It would seem that for curare there is no possible way of becoming habituated.

CHAPTER XXXI.

Force of Habit.

Force of habit; frequent repetition; influence of organic predisposition, or of local organic condition.

GENTLEMEN:

I come now to speak of the theory of "force of habit." How is it possible that an organism at first so impressionable tolerates a drug with ever increasing facility, so that in the end it appears insensible to doses which might bring on grave accidents? Several hypotheses might be made, and it is very probable that the different hypotheses find application simultaneous, or by groups, in the various cases.

It may be supposed that the destruction of the active substance to which an individual becomes accustomed is effected with more and more facility. It may be supposed that the destruction becoming more and more rapid, there never enters a sufficient quantity of the substance into the circulation and into the tissues, to produce the poisonous effects of the first doses. It would seem, from this hypothesis, that carnivorous animals, for instance, might, in the end, through force of habit, acquire the same immunity against substances such as the alkaloids, which herbivorous animals always possess. For it is remarkable that when the action of vegetable poisons is studied on rabbits, on the goat and in ruminating animals, it is seen that there is no great difference of action, whether the poison is introduced under the skin or into the circulatory system; while in carnivora the action differs according to the mode of introduction. It might have been thought, otherwise, that it is through the rapid destruction of the substance in the primæ viæ that herbivorous animals escape

the poisonous action of such vegetable poisons; it can be easily understood that with greater activity of digestion the poisons may be more rapidly digested. Probably, also, the subjects who become habituated eliminate the poison with increasing rapidity.

You all know the importance of elimination; it is through its agency that we ordinarily escape the poisonous action of substances introduced into the economy. Its activity becoming more and more considerable as the system reacts, it is the function through which the individual escapes from the consequences of the action of a poison.

There is also another hypothesis; it is that the energy of reaction becomes more and more marked. When you are exposed to cold, you will at first be depressed, and later become excited; you thus react, and efface by this reaction the positive phenomena of the action of cold. The cold occasions at the periphery a diminution of temperature, corrugation of the skin, a more or less energetic contraction of the cutaneous dartos, and following these phenomena, more or less vivid redness will be observed to appear almost instantly, which is due to the dilatation of the capillaries a moment before retracted; then calorification becomes exalted, and relaxation of the tissues ensues. What you here see produced through the action of an external agent is equally produced by substances introduced into the interior of the economy.

Thus, the susceptibility, as regards foreign substances, may become duller little by little, and the sensibility becoming gradually diminished, the substance, which at first was very poisonous, because of the great impression it produced, slips along, as it were, and later passes unperceived. I repeat, these are the four hypotheses that can be made; they are all plausible, and I think that the whole four should be adopted to explain this immunity through force of habit. This presupposes on the part of the economy a remarkable faculty of adaptation, which might be expressed by the term, "organic elasticity." It is a very general phenomenon. You have but to examine the two kingdoms and you will see that it exists everywhere. It is through this elasticity that human

beings can exist over so extensive an area; and that they can by either functional or structural modifications, place themselves in harmony with the conditions under which they are called upon to live.

Man can live almost everywhere. When we go into tropical countries we shelter ourselves from the excessive heat by currents of air; in cold countries by other artifices. We thus escape great extremes of temperature. I do not pretend that in every case we adapt ourselves to the circumstances; but you will observe the curious phenomena of functional modifications on the one hand, and nutritive modifications on the other. When these modifications are further accentuated, when they are, as it were, imprinted on a race, then you have created a new race, which might with propriety be called a species.

For instance, a man from the North goes into a tropical country; see how interesting are the modifications he undergoes. This man, of rosy complexion, becomes pale; what does that signify? that he loses blood globules; showing that the number needed for hæmatosis becomes less considerable. It is one way of becoming adapted to a climate where there is no further need of so much combustion to create force, since the general temperature almost equals that of the body.

Why do southern races become colored? Because of all the vibrations of imponderable fluids, the most active is luminous vibration, and to diminish this vibration it is necessary to extinguish it. This is why a pigment, becoming gradually thicker, is produced at the surface of the skin and prevents solar radiation from producing the disagreeable effects it is capable of causing. It is the same for the modifications of the hair follicles. The bulb increases gradually in proportion with the needs.

There are other forms of adaptation: Nutritive and functional modifications are produced; for instance, there may be a diminution in the activity of the respiratory apparatus and an augmentation of that of the biliary apparatus. Why? Because there is less to be burned, and a large quantity of unburned material to be eliminated under the influence of an alimentation

which is not always in equilibrium with the needs of the economy.

Consider some simple facts relating to habit: A subject has been confined to bed, in the horizontal position, for a number of days. He leaves the bed, and at the moment he rises his legs become violet. This signifies that there is no longer equilibrium between the muscular tension of the inferior limbs and the pressure the vessels are required to support. When he has passed a few hours in the erect position equilibrium is established. Again, the oftener the action of the cold shower bath is repeated, the quicker reaction takes place. At first precautions are necessary; later the subject reacts under the shower bath, the reaction being somewhat excessive, and finally the patient becomes entirely accustomed to it.

It would seem, then, that therapeutic habit is an equilibrium established between the intensity of the action of a medicament and the reaction of the system. It is a tolerance which becomes established after a period of time. But this expression "tolerance" awakens other ideas in the minds of many physicians. It is an entirely different affair from that which I have just explained to you; especially by one school, that of Rasori. The partisans of Rasori give this example: When tartar emetic is given in small doses, it induces nausea and vomiting; and when the dose is somewhat considerable and the subject very impressionable, there results emeto-cathartic effects of more intensity. Such are the proper effects which, according to them, belong to tartar emetic. If they are produced with certainty by middling doses, but are wanting when large doses are employed, Rasori designates this phenomenon by the name of *tolerance*. But it is to be remarked that even when emesis is wanting, other phenomena are produced, such as extreme prostration of strength, general frigidity, a cold and clammy sweat, a pulse either slow or very fast, depending on the manner of action of the medicament. Can this be called tolerance? Certainly not; it is a prostration of the system! It is no more tolerance than the state of powerlessness into which one pugilist throws another when he fells him by a blow.

The proof that it is a state of prostration is, that when the subject is attentively watched, it will be observed that at the same time with these phenomena I have just described there exists a state of stupor of the nervous system, and a general prostration of forces, so much so that the patient recovers with difficulty. There is another proof which will show you that it is not a tolerance, but rather a prostration of the organism. Generally you will not go so far with the remedy as to produce the degree of stupor and of prostration which simulates tolerance, unless the patient first suffers from vomiting and evacuations from the stomach and rectum. These efforts of vomiting require considerable energy of all the muscles of respiration and all the powers accessory thereto; consequently, I repeat, there is loss of substance and strength. This is why these phenomena never appear suddenly. It is not always in a pneumonia that tolerance can be immediately obtained, even in old women. I have noted this at the Salpetrière hospital, where from eighty centigrams to one gram of tartar emetic were sometimes given.

I have seen, in such cases, pustules formed in the stomach, and death caused by tartar emetic. I say, that even for aged women, consequently, under conditions of diminution of strength, this tolerance was never observed to become established immediately. When, then, does it become established? When the subjects are entirely worn out, as in very grave forms of pneumonia, as typhoid pneumonia.

I have often remarked, and I make the observation almost daily at the hospital, that it is impossible to induce emesis in subjects who are in an adynamic state. Why? Simply because to vomit requires considerable strength.

What I have just said to you of tartar emetic, is observed also with digitalis. With feeble doses of ten centigrams, morning and evening, an increase of tension is determined by increase of the contractility of the peripheral circulatory system, and particularly of the contractile power of the heart. If large doses are given, they determine widely different effects, as irregularity, extreme precipitation and difficulty of the circulation, increase

of the œdema, even cyanosis, and finally phenomena of intense gravity. But this is, again, some will say, effected through tolerance. No; digitalis has, as it were, exceeded the strength of resistance and occasioned true poisoning instead of its ordinary effects.

Nevertheless, there is a veritable tolerance which may become immediately established, and which is, as it were, a habit adopted without requiring time. This true tolerance merits study. Here is how it may be understood: it results from the more or less considerable resistance opposed by our organism to the action of modifying agents foreign to it; and which act as medicaments. This tolerance is of two kinds, either passive or active. You will see that these distinctions are useful.

In the first class may be considered the different phenomena due to the active resistance of the system. There are those phenomena of reaction of which I have already spoken; reaction of greater or less intensity, which comes on suddenly, effacing all at once the immediate effects of remedial agents, or of medicaments. Thus, we react against cold, or the causes of great depression; or against heat and the effects of stimulants, as by perspiration, which is a means of reëstablishing equilibrium between the internal and external heat. Then there are those phenomena of destruction by means of combustion; or again, destruction by means of products furnished by the economy, which are a chemical means of producing alteration of noxious substances. Finally, there is more or less rapid elimination, which always occurs.

The passive means of resistance are, on one hand, non-destruction of the substance, and on the other, default of absorption.

It would seem that there are cases in which, before there has elapsed sufficient time for the patient to become habituated, there exists absolute resistance to the absorption of active substances; in other cases, through the diffusion of the active substance in a large body the phenomena produced are very limited and may pass unperceived.

If, for instance, into a large organism is introduced the same quantity of substance which generally produces active effects in

a small subject, it is clear that the quantity producing active effects in the second case may produce none at all in the first.

What I have said here of size, may be said of various ages of life. We will return to this part of the subject in considering the various doses which shall be given at different ages, and for each sex. At present I wish to call your attention to the difference between the new-born being and the adult. The same dose, other things being equal, introduced into the small organism, should there determine more considerable effects than in the organism twenty times larger, and in whom the quantity of blood destined to receive the substance is twenty times greater.

There is also a form of tolerance which is established without delay through a diminution of susceptibility, through an inertia manifested by the system in presence of the active substance, and which varies with the mode of action of different substances. Consider, for instance, alcoholic liquids: there are nations which are sober, and others again which are prone to alcoholic excesses, by their constitutions.

It must be admitted that the habit of sobriety or alcoholic excess has considerable relation with the exigencies of the climate, and with the impressions produced by the surroundings on the economy. This is so true, that the inhabitants of southern zones who travel in northern climates soon acquire the habit of drinking like northern nations. It is not through any need that they thus imbibe, but because of the difference in the intensity of the effects, which enables them to drink much.

Thus, every traveler who has been in the northern part of Russia will tell you that when the cold is very intense, brandy can be taken like water, and without the individual being aware that he is drinking an alcoholic liquid. This is the true tolerance; under the influence of the anæsthetic state of the different surfaces with which the remedial agents come in contact, there is diminution of susceptibility to it. It is the same for the influence of conditions of temperature. According to the condition of the individual, the rays of the sun may determine either painful accidents, or not be felt.

If a person is in good health, with no tendency to vascular dilatation, if there is no part of the organism in an inflammatory state, he may, with impunity, expose himself to the sun's rays. If, on the contrary, he is already subject to cephalalgia through congestion, he cannot do so with safety.

There are other facts yet more singular. It would seem, at first thought, that every one would be equally susceptible to the action of a sinapism or of a blister. Yet, there are individuals who do not feel the action of cantharides. I have observed such cases. I recall to mind a poor lady affected with a stricture of the descending colon. I wished, one day, to produce vesication, but no blister would take effect. Two or three years from that time she proved susceptible to their action.

It is the same with sinapisms. There are cases where the strongest produce no redness or pricking. This happens in certain conditions. Rules may be given whereby it may be predicted which subjects will prove impressionable, and which indifferent to their action. Thus, nervous, hysterical women, in whom there exists true analgesia, will not prove so susceptible to the action of a sinapism as others. Sometimes they will produce some redness, but no pain, which is one of the conditions of their revulsive action. What I have said concerning nervous women may also be said of subjects presenting analgesia generally.

Thus, in subjects with lead poisoning, irritating substances have less effect in the regions where there is analgesia than in other regions which possess sensibility for pain. Take opium and belladonna. Some patients are susceptible to the effects of one, others are more affected by the other.

It may be anticipated which subjects will prove tolerant for opium, and which for belladonna. A subject having the pupil large, vascular retraction, with great tension and active contractility of the vessels, will tolerate opium in proportion as these conditions are more distinctly marked.

Inversely, if the pupils are contracted, with great vascular development in the brain, the subject will prove more tolerant for belladonna. This is so true that adults in general are little suscep-

tible to the action of opium, while they are very impressionable to the action of belladonna; while in children the susceptibility for opium is extreme, and very much lessened for belladonna.

What is the difference? It is this: in children the cortical substance of the brain is so vascular that it is red, and novices always believe in the existence of inflammation when they observe this state; in fact, little is necessary to cause this limit to be passed, and for the state of vascularity, normally very considerable but physiological at this age, to become exaggerated, excessive and morbid. Hence, children cannot tolerate the smallest dose of laudanum or opium. On the contrary, you may give them almost as much belladonna as to an adult.

This difference for different ages is presented also between individuals of the same age, according to the condition they may happen to be in. For opium, for instance, this general rule may be laid down: that tolerance becomes more immediately established when the subject suffers from great pain, accompanied by the vascular retraction of which we have spoken a short time since. One, at least, of these conditions is necessary for tolerance to become established. Thus patients in tetanus take enormous doses of opium with impunity. It is the same for individuals afflicted with neuralgic pains, particularly in certain conditions.

There are two species of neuralgia: the one due to simple modifications of nerves, the other congestive neuralgia, true neuritis, as Bouillaud would call it.

One form yields to the action of sulphate of quinine and the other to opium.

Certain states of obstinate insomnia are due to a state of permanent ischæmia of the cerebral substance. You may in such cases give extremely large doses of opium without producing any symptom of morphinism. This is in complete opposition with what is observed in other cases, where the subjects are predisposed to cerebral congestion, to whom you cannot administer any notable dose of opium without augmenting the symptoms, or without causing them to reappear if they were on the point of disappearing.

There are other classes of remedies which present these same conditions of tolerance or intolerance, even immediately after being taken. Diuretics act when there exists a state of great tension, a condition of general ischæmia, particularly marked in the kidneys.

When you give diuretics in conditions opposed to their opportunity of action, they pass just as if they had no such action, and without producing their usual effects.

Emetics present conditions of tolerance and intolerance; when you give even very feeble doses of ipecac, for the purpose of determining, for instance, hypercrinesis of the bronchial tubes, you may provoke vomiting with great facility if there is already existing a state of irritation of the gastric mucous membrane.

In opposite conditions, you may give not only large doses of ipecacuanha, but also of tartar emetic, without any effect. For instance, there is nothing so difficult as to induce emesis in delirium tremens. I cannot give you the reason, but the fact is so. It recalls a practice common among certain physicians, and to which I myself have recourse occasionally, which consists in giving alcoholic preparations in large doses, to arrest vomiting.

We will now consider a point which touches on the question of tolerance. I said to you, that through certain organic predispositions there is either exaggeration or diminution of the effects of medicaments: and that this diminution might be carried so far that the medicament might appear to be completely tolerated. There are other circumstances, in which, under the influence of this same predisposition, remedial effects are obtained opposed to those desired, and which are generally produced by the remedy.

Take, for instance, opium; you know that generally it is a means of diminishing the secretions; under certain circumstances it has an opposite action, augmenting them.

You have, for instance, a patient suffering from the pains of lead colic. While these pains last, there exists profound ischæmia of all the abdominal organs, so marked that secretion is impossible. You give opium; not only it calms the pain, but it produces a certain vascularity of this apparatus; and through

this return of blood to the parts there is an increase in the secretion of intestinal mucus.

Take an individual in whom diuresis is diminished or almost suppressed through the dimunition of the afflux of blood to the kidneys. You give him opium, you cause the disappearance of this state of ischæmia, you induce active secretion, and the kidneys recommence to perform their functions. This fact is exceptional, but is observed from time to time.

CHAPTER XXXII.

Intolerance.

Intolerance; adjuvants; synergetic and antagonistic substances; counter-poisons and antidotes.

GENTLEMEN:

In considering the various conditions under which tolerance is observed, I have portrayed indirectly the history of *intolerance.* It suffices to reverse the picture, to take the opposite view of various peculiarities which I have indicated as inducing tolerance, in order to have the conditions under which intolerance is generally observed. When we study the phenomena of intolerance, we observe that in certain conditions of the vascular and nervous system, any species of stimulant becomes an irritant, or may induce inflammation and fever. Thus, you will see patients suffering from a dyspeptic state, accompanied by slight inflammation of the primæ viæ, who cannot swallow, without suffering from painful irritation, even a spoonful of wine, a state of things absolutely preventing the use of a liquor which might aid in reëstablishing health.

Again, there are analogous conditions of the central nervous system; there are subjects so predisposed to hyperæmia of the brain that the smallest portion of wine is capable of exciting intense cephalalgia. You will also meet with subjects in whom the predisposition to vomit is so imminent, that you cannot introduce any substance in the smallest degree stimulating, without causing vomiting, alimentary substances even being rejected as though they were poisons.

You will again see, in certain conditions of cutaneous irritability, that any topical application, no matter of how mild a character, will excite redness, irritation, and a slight degree of

eczema. If the topical application is at all irritating, it will cause the formation of phlyctenæ and bullæ, and give rise to an inflammatory state resembling lymphangitis.

In other subjects, where there exists an increase in the excito-motor activity of the medulla, nothing can be given without inducing symptoms of irritation of this organ; certain subjects are so susceptible to the effects of belladonna, that a milligram of the neutral sulphate of atropine induces mydriasis and even delirium.

I have already cited to you analogous facts as regards morphine. There are circumstances where these excessive effects can be explained. This is not very difficult for morphine, but more so for atropine.

For morphine it may be foreseen that subjects having a tendency to hyperæmia of the nervous centres will be liable to excessive effects on the nervous system; on this account the effects are so considerable in children.

I have said that under certain circumstances medicines produce effects different from those desired, and often completely unexpected.

Thus, when certain agents are administered, such as digitalis, instead of the slowing-up of the pulse, we may have increase of tension and force of cardiac propulsion; in a word, instead of the phenomena which are usually presented in subjects, exactly the opposite is observed. In such cases, the more you insist on the use of even moderate doses of digitalis, the more marked will the symptoms of asystole become. What does this prove? It proves that at a certain moment asystole consists not only in ataxia, but that there is at that moment a paralysis of the different nerves—numerous, as you are aware—which animate the central organ of circulation. If at this moment you intervene with digitalis, you do but augment the state of asystole.

I have spoken to you of some cases which appear paradoxical, and where phenomena entirely unexpected occur. I cited to you opium, which is an agent capable of inducing hypercrinesis, and which, in certain cases, is a means of augmenting the intestinal

secretions; for instance, in dry colic, where it calms the pain and also favors the return of the intestinal secretions, and even of the secretions of the glands annexed to the digestive tube, as the liver. I have explained to you the rationale of this action.

Something just as paradoxical can be observed with purgatives. When you have decided that it is necessary to purge a patient, you may make use of drastic purgatives. But there are cases where the irritability is very considerable, in which you will not only be unable to produce the desired purgative effects, but you will augment the constipation. If, on the other hand, you prescribe very mild purgatives, such as castor oil, the saline purgatives, such as solutions of sulphate of soda, and the bitter mineral waters, then you will obtain satisfactory results. What has happened? In these cases there existed so much irritability, that, under the influence of the drastics, you have provoked true phlogosis and not a slight irritation; and, as you know, always when an inflammation is intense, not only is there not increase of secretion, but it dries up. You have but to observe patients who contract a severe cold; they commence by suffering from great heat about the chest, with absolute lack of secretion. The day when secretion takes place, when there is bronchial catarrh, that day inflammation is already diminished. These phenomena serve to explain to you in what manner the drastics act.

From the array of facts which I have passed in review in these two lectures, the following rule may be drawn: *The effects of remedial agents are more intense when the economy is already turned in the direction towards which the medicaments tend to impel it; the effects, on the contrary, are less intense, or what amounts to the same, tolerance is greatest, when the economy is turned in the direction opposed to that toward which the remedial agent has a tendency to impel it.*

Thus, if you have a subject in a state of ischæmia, and if you introduce substances capable of inducing hyperæmia, he will resist the action of the medicaments. If, on the contrary, he was already in a condition resembling that in which the remedial agent would

place him, then the action of the medicament is intense, and toxic phenomena are induced with extreme facility.

These deviations, these organic predispositions, have diverse origins. A subject may be in a state of ischæmia or of anæmia; or in a condition favorable to phlogosis, and to hyperæmia, through natural predisposition, as in subjects who have an inherited congestive tendency; or the individual may have acquired these deviations from the natural state in virtue of entirely artificial conditions, and it may be that remedial agents, poisonous substances, or the conditions under which he has lived, have induced them.

Here, then, we find ourselves in the presence of what is termed the *synergia* of substances, or on the contrary, their *antagonism.* That is, we have to deal with circumstances in which there exists, as it were, an artificial malady produced by a remedial agent given previously, and which aids in the action, or on the contrary opposes the effects produced by another remedial substance.

I will give you a succinct history of antagonism, because it is indispensable to the art of prescribing, and to the comprehension of the phenomena induced when you administer antidotes; or again, when you make use in the same prescription of substances antagonistic in action.

I will first speak of the mode of action of *adjuvant* substances, or of the substances which have an action synergetic with that of the principal agents that you have decided to employ. There are here very diverse modes of action, some of which you already know, because they are constantly observed when the history of medicaments is studied. There are accessory or secondary substances which act the part of chemical adjuvants. These substances serve, for instance, to aid in the solution, transformation, and chemical metamorphosis of the substance destined to be absorbed, and consequently favor its absorption. Thus, acids serve to favor the solution of bases, and reciprocally the bases that of the acids.

In the second place, there is on the part of accessory substances, which act as adjuvants, the power of preventing the

topical action from passing a certain limit, and consequently they aid to prevent diffusion of the substances. You know, when the topical action is very irritating, absorption is not well performed. Consequently, we must in some cases reduce the intensity of the topical effects in order to favor absorption.

To accomplish this, various expedients are employed as mechanical means, as when the substance is enveloped in gum, which prevents the active substance from coming in contact, in too large quantity at a time, with the gastric mucus. In other cases the adjuvant, or the corrective, constitutes with the substance a combination which renders it less irritating. Thus, aloes and scammony entering into combination with medicinal soap, divide the base with this kind of acid, and there results a substance of which the affinities are partly satisfied, and which is less irritating for the mucous membrane on which it is applied.

There are other substances intended to diminish pain, topical irritation, and the action of vomiting, which occurs very often on the introduction of medicaments. These are correctives *par excellence*, and such substances are very numerous. You employ, sometimes, capsules containing ether, which you administer just before a medicament capable of producing a pain in the stomach; or oftener you give a few drops of laudanum; on other occasions a compound pill, in which you will add narcotic substances, whose effects will increase those of the principal remedy. You will also give waters charged with gases, or the mineral waters which contain gases in solution, which are of a nature to prevent vomiting in persons disposed to it.

There are other correctives very frequently employed, which are found in all ancient prescriptions, and which are, perhaps, somewhat too much neglected to-day.

Empiricism has demonstrated that aromatic substances are eminently calculated to aid in the passage of a great number of active substances; that the taste of the tinctures of cinnamon, of ginger and of cardamon, is excellent for this purpose. When you give, for instance, preparation of colchicum, if you desire these preparations to be absorbed, associate them always with some one of

the aromatics I have mentioned, and which prevent the colchicum from producing local effects on the stomach, and through that nausea and vomiting, and also prevent the topical effects on the digestive tube which are often the cause of diarrhœa.

There are substances which augment the action of the principal remedy, by opening, as it were, the passages of elimination. Thus, if you wish to induce transpiration by the aid of aromatic substances combined with acetate of ammonia, it is well to associate opium with them; in certain cases it is of benefit to associate ipecacuanha with them. Why? You will say that opium is diaphoretic of itself, and passes in part by the skin, that it even determines eruptions; but it is not a very powerful diaphoretic; the preparations of ammonia are certainly more energetic, in this respect, than opium. Yet, when you wish to have as abundant transpiration as possible, through the old means of the materia medica, it will be of benefit to combine the action of the diaphoretics with that of opium, or of ipecacuanha, for opium has a tendency to relax the vessels of the skin, lights up the face, and tends to render more active the cutaneous secretions.

Ipecacuanha has a somewhat analogous effect, but accomplishes it by a widely different mechanism. Employed in small doses, as in Dover's powder, by the state of nausea into which it throws the patient, it causes a tendency to perspiration. Every one has remarked that those who suffer from nausea have such abundant transpiration that the sweat stands in beads on the face.

Digitalis produces entirely contrary effects, through the tension it produces and the more energetic cardiac action. It has a tendency to induce diuresis, and it does this by itself and without the aid of any other substance. But, if you wish to have passed by the kidneys a large quantity of a remedy intended to modify the mucous lining of the bladder, you may add digitalis to the mixture, and you will obtain more considerable diuresis; while if you add opium there will be greater tendency to pass by the skin.

There is another modification of this directing action presented by some substances.

I have already spoken of what I term directive bodies, which sometimes seem to give their veto to the passage of a substance, and in other cases cause it to pass by a route which it never follows of itself. I instanced that camphor prevents cantharides from passing by the kidneys. I cited to you also iodine, which, combined with iron, compels the iron to pass by the salivary glands, although it never follows this route except under these particular conditions. You do not observe this with the sulphate or carbonate of iron. Another condition in which secondary, or accessory substances may add something to the effects of the principal substance, is when these ingredients, although having less effect than the principal substance, act exactly in the same manner, and are true synergics, adding to the effect of the principal substance.

The bitter tonics afford an example. It is remarkable to observe that bitters, no matter what their origin, exercise always the same action, the only difference being in the intensity. Thus, when you use a concentrated solution of bitter principles, as for instance of quassia amara, and introduce it under the skin of a frog, you will bring on tetanus, exactly as with strychnine.

Analogous facts are observed with the other bitter principles, so that it would seem that there is simply a decreasing curve from the highest, that is strychnine, down to the light bitters furnished by indigenous plants. It is clear that if you associate these different substances, the various effects are combined, and an active compound is obtained.

Emetics may be divided into two categories: those which cause vomiting by acting on the periphery, and those which, on the contrary, act on the bulb; those which act in the manner of gastritis and those which act in the manner of meningitis.

These emetics can be associated. A common prescription is one gram and a half of ipecacuanha with fifty centigrams of tartar emetic. This association is a good one, and induces vomiting with more certainty than either separately. In the same way might be associated the various emetics which act on the bulb. The exosmotic purgatives aid each other mutually, as you are

aware; they are almost always associated either in the prescriptions which we order, or naturally in the bitter mineral waters, which have nearly all the same composition, and spring, for that matter, from the same kind of strata.

Another occasion where an auxiliary effect is obtained is when we associate narcotics which do not act in an identical manner, but have at least analogous action. One kind affects one portion of the nervous system, the others another division.

Take, for instance, a prescription which contains belladonna, opium, ether, and cherry-laurel water; these substances, which, when alone, affect distinct divisions of the nervous system, when associated, act together and produce similar general effects.

Opium acts with preference on the cerebral hemispheres; belladonna produces more notable effects on the organ of vision and predisposes also to slumber; ether is a means of diminishing general sensibility; cherry-laurel water exercises its influence on hæmatosis. But by this combination a subject is rendered calm with much more facility than if any one of them was used alone. This is a case where substances differing from each other in effects act in unison when combined.

You will find the same to be true of what are called complete purgatives. There are purgatives which act on the contractility of the intestine; there are others which act by irritating the mucous membrane, and which augment its secretion; others which act by irritating the liver, and consequently produce hepatic secretion. You may combine all these with substances which are particularly exosmotics. If you associate these agents, you have a complete purgative, like the black draught of the codex (French), which often acts much better than a simple purgative.

By this association of three species of purgatives, results of more certainty are obtained with more facility and less cost than with a drastic of great energy but acting in one way only.

There are, finally, cases in which substances which are associated each affect one organ only, or one emunctory, and each acts independently; but from the united action of all there results increased therapeutic effects than from any one alone.

Take, for instance, a case of cachexia with dropsy; we give tonics to reëstablish the forces and render the patient more susceptible to the action of remedies; then may be given purgatives and diuretics, which produce the evacuation of the water held in the cellular tissue and the serous cavities.

Take, again, the dartrous diathesis; we give, it may be, arsenic, but at the same time we employ various means to act on the skin and on the digestive tube, in order to produce more or less intense revulsion toward these organs.

Take, again, a syphilitic patient; at the same time that we give a substance capable of causing the disappearance of the disease, we give, also, tonics, to prevent the patient from losing in general health through the influence of the virus.

In meningitis we give bromide of potassium and calomel, which is an agent of antiplastic action; but at the same time we produce revulsion by irritating applications to the extremities, where we place either sinapisms or blisters. All these means concur to the same end. These substances are not really synergic; they do not become so unless we take the organism to be a living unity; it is through the solidarity of the various organs that we obtain revulsive effects, because the sympathy which exists between the various organs is the cause that the action exercised on one is felt in the others; and as it would seem that at any given moment we have but a certain quantity of force, when revulsion or derivation or marked secretory irritation is induced, the whole system is affected, and any morbid process going on in another part is checked, because it has not the necessary materials for its development; this is one manner of explaining the effects of revulsion.

In another class of cases there are remedial substances which oppose obstacles to the action of the principal agent. These are said to be antagonists; they may be distinguished into chemical and pharmaco-dynamic antagonists.

The chemical antagonists were alone known to those who have preceded us. They embrace those substances known to-day as counter-poisons. The recent acquisitions of science have shown us also antagonistic effects through pharmaco-dynamic action.

From this what is called therapeutic antagonism had its origin. I have proposed to term it *antidotism*, because the other term already exists in pathology. There are, then, chemical antagonists and pharmaco-dynamic antagonists.

The number of cases where chemical antagonists show their power is considerable. For instance, we introduce into the stomach a substance destined to act by its alkaline qualities; it comes in contact with chlorhydric acid and becomes a salt. In other cases we give phosphoric acid; it comes in contact in the stomach with alkaline substances, combines with them, and then the urine hardly reveals its presence.

In other cases, soluble salts are introduced into the primæ viæ, where they meet with chloride of sodium, and form insoluble salts.

In the same way tartar emetic may be destroyed, as also the alkaloids. Thus, there are quite a number of circumstances by which the action of medicaments is prevented.

But dynamic antagonism, or real antidotism is much more interesting. Without any doubt the antagonistic value of varieties of substances has been much exaggerated. Therapeutic antagonism is frequent, but has not the value usually accorded to it. It may be said that there exists hardly one case in which two substances having different actions may become directly opposed one to the other, so as to neutralize each other regularly and definitely.

There is, perhaps, one exception; the case of eserine and atropia. It was known from the time Calabar bean was introduced, that it was a myotic agent, and it must have been immediately understood that it was the opposite of belladonna. Researches were made regarding the conditions under which this antagonism was produced, by Bourneville, in France, and by Fraser, in England. What happens is this: atropine, as you know, diminishes the activity of the pneumogastric; eserine, on the contrary, augments its power. In other words, eserine diminishes the number of cardiac pulsations, while atropine singularly augments them. Eserine augments tension, atropine di-

minishes it. These are, for that matter, correlative facts. According to Marcy, tension is diminished when the number of pulsations is augmented. Eserine augments the secretion of the salivary glands, as also of the lachrymal, intestinal and renal glands. Atropine diminishes all the secretions. Atropine diminishes the contractility of arteries; eserine that of the veins. Atropine produces mydriasis and eserine myosis. It may be said that opposition exists at every point between the two.

Notwithstanding this, there are circumstances which demonstrate that this antagonism is not so absolute as might be believed. If eserine often diminishes the contractility of the veins, in a certain number of cases it augments it when given in small doses. If the myosis determined by eserine is placed in comparison with the mydriasis determined by atropine, there is no equilibrium between the two. The myosis is feebler than the mydriasis, and this last is of longer duration. Consequently, you can conclude that the two substances cannot serve reciprocally as antidotes. What then is not obtained in this perfect case, you most certainly will not have in other cases, when, for instance, belladonna is compared with opium.

CHAPTER XXXIII.

Antagonism between Morphine and Atropine.

Therapeutic antagonism in general.

GENTLEMEN:

Much has been said concerning the antagonism between morphine and atropine.

Von Graefe was the first to administer belladonna in cerebral affections presenting myosis, under the impression that since belladonna determines mydriasis, when there exists spontaneously a morbid state accompanied by contraction of the pupil belladonna should give good effects; and inversely, he gives opium when there existed dilatation of the pupil. He thus obtained therapeutic results of great value. I have followed this example, and in many cases I have had reason to be well satisfied with the results. Recently, I had, at the Beaujon Hospital, a woman brought in in a state of delirium; five centigrams of morphine had been injected hypodermically, and internally she had taken five grams of chloral and I do not know how much bromide of potassium.

When I arrived to make the morning visit she was in a state of violent agitation; her eyes wild and injected, the pupils contracted. I considered that in such a case opium would not be of benefit; that a substance capable of dilating the pupil would be more appropriate than atropia. But as I was experimenting with duboisia at the time, which is an alkaloid which resembles atropia and which presents immense activity of action, I injected a milligram of it hypodermically. In the space of ten minutes calm was restored, the agitation and vociferation of the patient

ceased, and when we returned to her a short time afterward the pupils were dilated, her eyes less injected, and when it was necessary, shortly after, to remove her, it was with great difficulty she was awakened. You can see that this was a real triumph. One must thus be governed by the anatomical conditions in which the central organ of the nervous system is found.

I repeat, this antagonism is of benefit to us; it shows us the conditions under which certain means should be employed, and it teaches us under what conditions we may oppose morphine with atropia, and the reverse.

But there should be no illusion on the subject; this antagonism is but partial. My regretted friend, Behier, who took up everything with passionate energy, had been struck by this partial antagonism, and went so far as to think, with many others, that this opposition was absolute; that it occurred in every case, and that, consequently, these two substances were veritable antagonists, and that from the moment the knowledge of this fact was known to science there was no further occasion for anxiety in poisoning by opium or morphine, since there existed a means of introducing these substances into the cellular tissue, and thus their effects can be always assured. This view is erroneous. It has been seen that this antagonism is not sustained when large doses are employed; toxic phenomena appear in such cases, even when the two drugs are simultaneously given; the symptoms of stupor appear to be more generalized, but they are not in the least diminished by the particular effects of either of the substances.

You will find in an excellent work—a book I cannot recommend too much to you, that of John Harley—excellent accounts of opium and belladonna. He demonstrates by a series of varied experiments, very well made, that not only there is no antagonism for elevated doses, but that even there is increase of effects; and so when considerable doses of atropia are employed to combat toxic morphinism, more rapid toxic effects and death with more certainty are produced.

You may ask how does it happen that the illusion has persisted so many years; and why the journals report cases in which

poisoning by laudanum has been efficaciously combated by atropia, or belladonna?

It is always the same story! Illusions prevail, because the natural course of diseases is ignored. Every observer has believed that excessively large doses of laudanum or of atropia are necessarily and fatally mortal! This has been believed so firmly, that the antagonism has been considered perfect, simply because the patients recover. A man is in a state of coma from opium; hypodermic injections of atropia are made; he recovers; is it a success for atropia? not at all.

One day, a druggist in the vicinity of the hospital St. Antoine brought us a woman who had just bought laudanum from him and had swallowed it in his presence. There had been sufficient laudanum taken to poison many persons. The terrified druggist carried the woman to the hospital; there they prepared to administer belladonna in large doses. The woman remained a time intoxicated; she then fell into a state of profound stupor, from which she did not revive for a long time. The interne, who had administered belladonna, was enchanted; he had recalled the poor woman to life. Unfortunately, this woman confessed that she was in the habit of taking laudanum, and that the dose was a trifle larger than she ordinarily took. In order to procure it, she caused prescriptions to be written, and thus she got large quantities of laudanum, which she drank, and which produced a sort of intoxication, followed by a slumber with dreams worthy of being sung by the Spanish poets. This woman was received later, at the Neckar Hospital, where she repeated what she had before said, that she drank laudanum as other people drink wine.

There is a case of poisoning by atropine, where there was no intervention, and which will show you that poisoning, even of the most violent kind, is often followed by recovery. One of my former patients, an advocate, was subject to violent attacks of cephalalgia. This, but a slight malady for individuals with much leisure, is of gravity for persons who are obliged to work on fixed days. He often asked me to rid him of this

headache. I prescribed a well regulated manner of living, with a little bromide of potash. One day, at a friend's house, he met a physician who said to him: "What! Professor Gubler cannot rid you of your headache! it can be done with ease!" The advocate did not wish to receive advice in a reception room; but one day, when I was in the country, he had an attack of headache, and as I could not come, he went to see his physician. He wrote his prescription, ordering ten centigrams of sulphate of atropine in thirty grams of water. He told him to take the mixture in doses of a teaspoonful until the headache had disappeared. My patient thought that a teaspoonful was very little, he took a dessertspoonful, that is, something like six or eight grams, of a solution containing ten centigrams in thirty grams. Hardly had he swallowed the liquid when he felt a strange sensation of malaise, and was seized with sudden delirium. He rose from the chair, entangled his foot in his paper basket, thinking he was in his bed, and fell. He remained thus until the next morning, no one having heard him fall; then, in the morning, feeling cold, he became conscious, but could not distinguish anything clearly. He recovered completely; I saw him the next evening; the pupils were even then much dilated, but there were no longer any signs of intoxication. Remember, that nothing was done to aid in his recovery. Are you acquainted with many cases of poisoning by atropine with so strong a dose? Three centigrams swallowed at once and in solution! When one has witnessed facts of this kind, he is not very apt to believe much in the story of the antidotism of atropia and morphine.

I would advise you not to place implicit confidence in such antidotism, and not to imagine that it is enough to give as large doses of atropine as has been taken of laudanum, in order to resuscitate the patient.

You see, then, here are two substances concerning which the doctrine of antagonism pushed sometimes as far as antidotism has been established.

These two substances are not true antidotes. In fact, in order that the antagonism should be complete, the reunion of a num-

ber of conditions, such as are almost never met with, is necessary. It would be necessary that they should enter into antagonism in all the organs on which the action of either one of the substances is affected. For if there is one point alone which escapes the action of the counter-poison, then you will, it is true, have determined contrary phenomena in certain favored organs; but you will also have permitted the progressive, excessive and fatal development of all the accidents in another organ.

I will take an example: You are acquainted with the effects of chloroform when administered by the respiratory passages. It first produces phenomena of excitation, then of stupor, and these phenomena follow each other in the following order: first, the cerebral hemispheres are affected, then the organs of special sense, hearing being the last sensation lost; after the hemispheres, it acts on the medulla. Later, and at an advanced stage, it acts on the bulb, on the origin of the pneumogastrics, or the "vital knob," as Flourens has called it.

Suppose that you are present at a case of poisoning by chloroform and that you have at hand strychnia. The chloroform has thrown the subject into a state of absolute relaxation; you call to mind that Claude Bernard has said strychnia is a means of reviving the movement, and of exciting in the highest degree the excito-motor force of the medulla: here is a fine occasion to employ the counter-poison. If you give the strychnia you will revive the voluntary muscles, you will much augment the power of the excito-motor action of the medulla; but you will not act on the bulbar centre in the medulla oblongata. But it is precisely this centre that is affected in accidents of such gravity, and it is through it that death ensues. When the organ holding in dependence the central organ of circulation and respiration is compromised, there is no time for delay.

You see, then, that it does not suffice to have a generalized antagonism; it is necessary that it be produced on every organ, and particularly in the organs essential to life. It is necessary, also, that the intensity of the action of the substance playing the

part of antagonist be adequate to neutralize the action of the noxious toxic substance.

For, finally, supposing that you have a perfect antagonist in a substance like, for instance, eserine for atropia, if you give a feeble dose of eserine, you will not combat the effects of a very large dose of atropine. This example shows that if you administer, in equivalent doses, a substance of which the action on the organs essential to life will not be equivalent to that of the poison, you have accomplished nothing. Thus, you will never succeed in calming poisoning by strychnia, through the aid of an alkaloid like solanin, which is less powerful than strychnia.

There must be opposition in all the organs, and the action of the two substances be equivalent, so that the antagonist be adequate to neutralize the effects of the toxic substance. The substances which are used as antidotes for each other must act in an inverse manner on the organs.

Take, for instance, tetanus; it is essentially characterized by tetanic rigidity, which is convulsive, and prolonged in all the muscles, and particularly in those which act in extension. But this rigidity, this state of contraction, which essentially constitutes tetanus, may be due to several conditions: it may depend on an increase in muscular contractility, or there may be greater irritability either of the motor or associated sensory nerves; or, again, it may result from the excessive augmentation of the excito-motor action of the medulla.

Instead of one of these conditions, there may be association of three or four of them. This admitted, you can understand why the hopes conceived regarding the good results of woorara, in spontaneous or artificial tetanus, have not been realized.

Vella (of Turin), having witnessed the experiments of Claude Bernard on woorara, inferred that, since it had placed the contractile system in a state of complete resolution, it would have the power of calming the symptoms in tetanus, and of opposing the action of strychnia. This inference is true if one be content with objective phenomena. That is, if you introduce woorara in sufficient quantity to combat the tetanic convulsions, observe,

these convulsions will lessen, and relaxation will ensue. Have you triumphed? Do you believe that your patient will recover because his muscles are somewhat softened? Not at all; although you have obtained a fine result as regards the contractions, the patient is no better, in most cases, because woorara acts but on one of the conditions of tetanus, and not on all.

What action, in fact, has woorara? We know its action through the experiments of Claude Bernard, and particularly through those of Vulpian. Woorara acts, if not entirely on the tissues of muscle alone, at least on the terminal expansions or terminal plates of the nerves in the muscles themselves. It is not possible to prove that the action is limited to the muscles; but through experiments very well made, it may be concluded that woorara does not act on the medulla, on the trunks of the nerves, not even on their peripheral divisions; so that it must be said that it acts on the muscles, or at most on the expansions of the peripheral nerve extremities.

If tetanus results not only from a local excitation of the muscles, which is not of great account in the production of the phenomena, not only from an excitation of the sensory nerves, which are the means of conduction of sensations from the periphery towards the central organ, but if it results also and particularly from the excessive increase in excito-motor activity of the medulla, you can understand that with woorara you produce no effect on the medulla, and consequently you accomplish but little.

On this account you see so often negative and so seldom positive results.

In order that an antagonistic substance prove efficacious it must act not only on the same division of the apparatus, but also it must act by an opposite mechanism to that by which the toxic substance acts. I spoke a short time since of a theory of more facility of nervous discharge than under ordinary conditions, as explaining tetanic spasms. Such an augmentation of the excito-motor activity of the medulla may depend on hyperæmia, with a state of nutrition more active than under normal conditions; also

on the possession of more considerable power on the part of the nervous system to become charged with force.

In such a case, if the antagonistic substance act in preventing hyperæmia, or by diminishing the combustions favorable to the overcharging of the nervous system; while, on the other hand, the toxic substance acts in an inverse manner, that is in augmenting the capacity of the medulla for excito-motor action; under such conditions you will have very incomplete results.

If, for instance, in a case where strychnia has excited the capacity of the medulla for action, you give ergot in order to diminish the quantity of blood going to the medulla, you will have done nothing but diminish the increase of excito-motor activity. You must find a substance having an action opposed to that of strychnia. This substance would seem to present itself in aconitin. This drug exercises an influence opposed to that of strychnia, and favors the incessant discharge from the medulla, just as if you gave a pointed form to the conductors of the electric machine, which would allow the electric fluid formed on the plate to escape. But aconitine would not give the effects expected from it; because it acts on other elements than the medulla, and would rather serve to add to the effects of strychnia itself.

Finally, the antagonistic action induced therapeutically should be of equal duration with the toxic action of the poison to which it is opposed. If you wish to combat the mydriasis produced by atropine by eserine, you will be obliged to have recourse to it at each instant. This is of sufficient facility when the eye is in question. But when one has to deal with an internal organ, it is more difficult; so that, supposing you have the reunion of all the conditions I have laid down, if the effects do not last after a few moments, the unfavorable symptoms will reappear. When the necessity of the reunion of all these various conditions in order to make a good antidote is taken into consideration, it it easily understood that there is none perfect in existence to-day, and I fear there never will be.

Nevertheless, the number of antagonistic substances is consid-

erable, and under the articles devoted to remedial agents a chapter is always placed containing the antidotes and adjuvants. Yes; the number of antagonists is immense; it may be said that there exist antidotes for all the substances which might be mentioned; only they exercise but partially their action, or they do not exercise it with the intensity necessary to prove true antidotes.

Take, for instance, opium; it has for antidotes, coffee, sulphate of quinine, strychnia, bromide of potassium, digitalis, etc. Is there one of these efficient? No. I have just shown you that belladonna is not. Coffee exercises its action on the cerebral cells, of which it augments the activity. It is, then, efficient for that part; but this does not prevent opium from continuing its effects on the other divisions of the nervous system, and on the sensory nerves. Sulphate of quinine is an antagonist of opium, without doubt. I showed it to be so, years ago, to a certain extent. While opium favors combustion and augments the volume of the capillaries, sulphate of quinine slightly opposes all these phenomena, but it does not prevent opium from manifesting its effects when it is employed in large doses. I could say as much for strychnia, digitalis, and bromide of potassium.

Antidotes are not wanting for strychnia. I mention opium, which is, at the same time, a remedy in spontaneous as in traumatic tetanus. Chloral is very good. But these are substances which narcotize particularly the sensory nervous system and the cerebral cells; they are hypnotics. Yet this does not prevent strychnia from exercising its peculiar influence on the spinal centre in a manner to produce tetanus.

There is, also, an antagonism existing between ergot and strychnia. This would be curious, and deserves to be further demonstrated.

CHAPTER XXXIV.

Antagonism (Continued).

Influence of the size of the body; of sex; of age; of temperament; of manner of living; of race; of climate.

GENTLEMEN:

We will turn to the antagonism between bromide and iodide of potassium. There exists a certain antidotism between the two substances. Bromide of potash produces a state of calm in all the organs; it is a sedative, while the other is an excitant; but these substances are synergic at other points of view, and they cannot, consequently, play the part of antagonists efficiently.

Take the substances which augment hæmatosis, which increase respiratory combustion; alkaline substances, in small doses; opium, by its action on the capillaries; the neutral salts, which in the serum of the blood play a part on which I have insisted. Compare them with others—the free acids, the essential oil of bitter almonds, the substances producing cyanosis in general, and arsenious acid, which has a calming action on the phenomena of hæmatosis; are these substances veritable antagonists? No; for you will often meet with certain ones among them which we use in opposition to each other, which, nevertheless, have effects which are similar.

Consider the plastic substances as opposed to the antiplastic; the chalybeates, perchloride of iron, the tonics in general, quinquina on one hand; on the other mercurial preparations and alkaline substances. These substances have a very different action on blood formation, but they are very far from being antagonists. Yet they are often combined in order to act on different regions; in general we may say there is a slight antagonism between a

great number of substances; or even that it is impossible to find any substance which does not present antagonism on some point when compared with any other. But the existence of extensive antagonism is an exceptional fact; some substances may modify the effects of certain others, but oftenest this antidotal action is so limited that it will never do to employ them in opposition to each other, as a means of cure.

When the older physicians employed antidotes, when, to-day, we recommend substances to combat poisoning, we have several ends in view, and we reach them by different means. Among the antidotes there are true counter-poisons capable of neutralizing chemical action. We have substances which act in provoking hypercrinesis—that is, energetic excretion, and then they open the issues for the elimination of the poison, whatever it may be.

There are other substances which exercise a stimulating action, and which have been considered, up to the present, simply as adjuvants, such as ipecacuanha. But the new experiments of Pasteur lead me to inquire if the stimulating action provoked in persons under the influence of a poison, if the stimulation recommended, for instance, in rattlesnake bite, has not another result, which is to elevate the temperature to such a point that it becomes impossible for the poison to germinate in the organism.

What is certain is, that all the remedies employed in tropical countries inhabited by venomous animals to combat such poisoning, count always among their properties the power of producing an artificial febrile state. Such are alcoholic substances, aromatics, and all those which the older physicians called alexipharmac agents.

Of like significance is the name *guaco*, in Mexico, which is that of all antidotes, no matter from what plant they come and of what family they may be. So, also, in Brazil, in all the vast extent of the basin of the Amazon, all the substances to which is attributed the property of combating poisoning are called *jaborandi*.

I add, that in the substances properly called antagonists are found combined in the same preparation properties capable of inducing hypercrinesis, with others inducing febrile action and diffusible stimulation.

Among the conditions which affect medicinal action is the size of the body. As a rule, the larger the subject, the more considerable the size of the body, the less marked will be the physiological and, consequently, the remedial effects of an active substance. The same dose is excessive for the child, moderate for the adult of ordinary stature, while for a giant it would be less than was needed.

Quételet, who has done much toward the statistics of physiology, published, in 1833, a table, established by numerous experiments. He places on one side men, on the other women; he takes them at all ages, he takes the mean of numerous weighings, and here are the results:—

At birth, a male infant weighs 3 kilos., 200 grams; a female infant, 2 kilograms. At one year: boy 9 kilos., 450 grams; girl 8 kilos., 790 grams. At two years: boy 11 kilos., 340 grams; girl 10 kilos., 670 grams.

Thus the weight is seen to increase in the two sexes, but there arrives a time, at about the age of 12 years, when the male child, who up to this time had always weighed more than the female child, loses somewhat in proportion, and equilibrium becomes established; at 12 years both weigh the same—29 kilos., 820 grams. At this period the weight of the young boy is slightly inferior to the half of what he will acquire when arrived at his maximum, which is 63 kilos., 670 grams, while the maximum for a woman is 56 kilos., 160 grams.

Consequently, at twelve years of age, the young girl weighs more than the half of what she will finally attain.

Weight augments up to the age of forty years for men; up to fifty years for women. In man, what augments principally are the muscular masses; while in women the augmentation is in fatty materials.

After these two epochs (forty years for men, and fifty for

women), weight diminishes, and at ninety years is 57 kilos. 830 grams for men, and 49 kilos. 330 grams for women.

These statistics may be applied to posology. If the dose for an adult be considered as unity, the dose under twenty years and up to fifteen is two-thirds; the dose at fourteen years is half; at seven years, one-third; at four years, one quarter; at two years, one-eighth; under that age, the twelfth, or the fifteenth.

Another rule is, if you employ a dose of 20 for an adult, you have but to diminish the dose by one part for each year toward childhood; but if you follow this rule, you will give doses which will prove too large.

If we consider the results shown by clinical experience, and bear in mind the importance of the size of the body, we should say that, in general, it is the weight of the individual which should serve as the basis for the dose. Here is how I would establish the doses at different ages: I would say, taking for point of departure the adult, the adult dose being considered as unity; at fifteen it will be two-thirds; at twelve years one-half; at two years one-sixth; at one year one-seventh; between birth and the end of the first year the dose would vary according to the substance employed, from one-tenth to one-twentieth. Beyond the age at which we place the limits of adult age, that is, after the forty-fifth year up to confirmed old age, the doses vary naturally. But here it is no longer a question of weight, as the weight does not change in any considerable degree; but it is according to the conditions of reaction presented by the economy that the proper dose is to be determined.

As for women, the absolute dose for man at unity may be diminished by one-eighth for them; the dose is, for that matter, variable.

Take, for instance, one gram of sulphate of quinine, the dose for an adult male; if you diminish it by one-eighth, you will have the dose that should be given. You may diminish it one-sixth, if you take into account the smaller proportion of blood in circulation.

For, although the determination of the amount of blood in the

human subject is difficult, there is reason to think that, while in the male there is six kilograms of blood, in the female there is but five. The difference in weight is not as considerable as the variation shown in the supposed quantity of blood in the male and female.

Here the question presents itself; should we consider the weight alone, or the quantity of blood? For those who admit that all the chemical and physiological changes take place in the blood, the blood would seem of main importance; as for us, for I hope you have come to partake my opinion, we think that the blood is not the usual theatre of action of remedial agents. We do not attach the same importance to it in a positive point of view; but what we would consider of more importance is the bulk of the solids in which the remedial substances will be diffused.

The larger the brain, the more morphia will be needed to induce sleep, to benumb the cells of the cortical substance. As much may be said for the other parenchymæ and for the other organs of the economy.

The blood has also its importance, but not so much as has been attributed to it by a number of physicians. It contains albumen, and consequently it is not merely a liquid mass in which the active substances will be diluted. Not only is it a diluent for the agent, but coming in contact with the plasma it envelops it, and this more markedly when the active substance is in feeble dose, and meets with a large proportion of blood. Thus, the blood is an agent producing division; it is a means of attenuating the action of the substance by surrounding it with albumen.

When the blood is in large proportion there is alteration of the remedial action; when it is in small proportion there is, on the contrary, increase in the intensity of action; and doses which, under certain weight, would not be poisonous for a vigorous subject, may prove so for individuals in an anæmic condition.

We will now commence the study of the complex influences which result from relation of age, sex, temperaments, races, mode

of life, and climate. You will see that the preliminary study into which we entered abridges the study of their relation.

At any age, what is to be most regarded is the stature and bulk. You see that all I have just said to you concerning the size or bulk had its utility. I am well aware, however, that all of importance is not included under the conditions of weight and bulk, and frequently great consideration must be paid to influences due to other anatomical and physiological conditions.

If we consider, for instance, infancy, we find special conditions which make infantile therapeutics differ considerably from the usual treatment in the adult. These are the physiological and anatomical conditions of the infant which cause differences in the doses. The infant has extreme susceptibility to impressions, which is the reason that the least excitation—a tooth pressing on the gum—induces spasmodic movements, which may indeed go as far as convulsions. Again, the infant has the cortical substance of the brain of so marked vascularity that it is rose-colored, and might be thought to be inflamed, when the normal state is not known. An infant lives on an aliment which is in a bulky form, that is milk; the child is apt to take too much, and from time to time vomiting, regurgitation and diarrhœa occur. These three circumstances explain many particulars offered by infantile therapeutics: thus, you cannot give them substances stimulating to the nervous system without causing various accidents; they can safely inhale ethereal substances; if you lay them on a mass of hops, they sleep as if under the influence of an anæsthetic; if you leave a bouquet of flowers in the room where a child is sleeping, they may have a toxic influence on it. In the same way, if you give a very young child a very small quantity of laudanum, accidents may follow; not only hypnotism, but profound, comatose stupor has been produced by two drops of laudanum.

There are also conditions which, in old age, cause variations in the action of medicaments. Thus, it is generally said that feebler doses are required for an old person. This is true, in

general, but in certain cases they require larger doses than an adult, for example, to induce perspiration or to provoke purgation.

As regards the sexes the difference is in great part due to the difference in weight, in the quantity of the blood in circulation, and to the richness of the blood.

In regard to the temperaments; these are influences explained by conditions which we have already determined; thus the greater quantity of blood present in persons of the sanguine temperament, the greater feebleness or strength, etc.

The predominance presented by certain organs should also be taken into consideration. Sometimes the nervous system is most predominant, and offers, in such cases, extreme susceptibility. Nervines should be given with precaution to such patients. Bilious people support purgatives very well, while others cannot tolerate them.

Now a few words concerning the manner of life of the individual, his habits and occupations.

Without speaking of occupations which may have some peculiar action, there are at least two great divisions to make: manual avocations and intellectual pursuits. Individuals leading a sedentary life become intolerant of most medicaments; those who have the blood rich, in whom the functions are better regulated, often present a resistance which may be termed tolerance. This is why more considerable doses are required for people in the country than for inhabitants of a large city.

Climatic influences are very complex; heat, cold, aliments, the productions of the soil, all these conditions induce variations in the state of health, and even of temperament and constitution. Then, again, there are poisons of all sorts which may exist in one climate and not in another. Climate itself acts, in general, by causing subjects to become vigorous, or, on the contrary, sallow and weakly. In the north plethoric individuals are frequent, in the south the greater portion are anæmic. Certain organs are apt also to acquire predominance of action. In hot climates, we know that the hepatic apparatus is apt to become predominant,

because there is imperfect combustion, and because most of the unconsumed materials are eliminated by the liver.

All these circumstances induce corresponding differences in the activity of medicaments, and in the direction or predilection which remedial agents manifest for certain organs.

I have already mentioned, in speaking of climates, the much greater capacity of the inhabitants of the north for alcoholic beverages. I could say to you, that general bleeding is better tolerated in the tropics than in the northern climates. It is on this account that the theories of Rasori had so much success in Italy and Greece; more considerable success than with us, more, in particular, than they had in the north.

I am myself an example of the utility of general bleeding. I fell once, in Italy, bathed in blood; I was carried to the hospital of Milan, where they bled me, two, three, even four times per diem; I was longer in recovering from the effects of the bleeding than from those of the wound.

I have often asked myself whether, if these bleedings had not been made, I should not have had tetanus, in such a month as July. General bleeding is well tolerated in southern climates. It is true that it is badly tolerated in marshy districts, because the paludal miasma reduces the inhabitants of such countries to a state of anæmia.

What should I say to you regarding the medical constitution reigning at any period? Medical constitutions are, after all, but climatic conditions, for they are due to poisons originating in the soil under the influence of temperature, poisons which might with propriety be termed telluric.

There are regions more favored by nature and at the same time more afflicted than the one in which we live, in this sense, that the natural productions are of more splendor, but the causes of death more numerous, giving rise to cholera, yellow fever, etc. Into such elements may be analyzed what is termed medical constitution, and which should be called nosogenetic constitution.

In regard to race, there are notable differences, as regards

remedial action, between individuals of the different races which people the globe; but positive facts are wanting.

In 1869 I remarked that the black race, the negro, has great tolerance for wounds of the abdomen; so much so that an impostor will sometimes open his abdomen before a multitude, in order that on his recovery he may be considered an inspired being, singled out by divine interposition. All those who have sufficient daring to do it recover. I warrant you that you could not do as much, and that if you plunged a knife into your abdomen you would infallibly succumb to the wound.

Dr. Thaly,* in a recent paper, establishes the fact that negroes support enormous doses of tartar emetic; that one gram per diem may be given to them without producing more effect than is obtained from five centigrams with us.

There are also considerable differences, at the present time well recognized, between the different races, as regards the action of substances capable of inducing drunkenness.

Thus with us, with the Caucasian races, and with Europeans in particular, alcoholic intoxication is mild, gay, amiable—there are exceptions, I am well aware—but there are races, such as the inhabitants of Java, of Borneo, of Sumatra, the Malays, in whom the effect of opium is gloomy, rendering them furious and murderous. A Malay can never become drunk without attacking individuals who have done him no ill. With us, on the contrary, the great proportion of drunkards are not at all dangerous.

This is not the effect of climate acting on the blood. The proof is that Europeans in the same countries, and the other races which inhabit India, do not suffer the same mania after taking alcohol. Even for drunkenness produced by other than alcoholic substances, you will find the fundamental difference which I have just indicated. No matter of what nature the poison, individuals of the Mongolian or Malay race become violent, quarrelsome, and manifest a desire to commit murder.

Finally, in regard to what is called idiosyncrasy: is it necessary to believe that certain individuals have the special privilege of

* Thaly; *Archives de Médecine Navale.*

reacting in a peculiar manner under the influence of a therapeutic agent, and so much so that there is no means of establishing any general rules? This is what empirical physicians desire to prove. No; idiosyncrasy cannot be admitted. All the modifications presented by individuals may be reduced to the conditions I have enumerated. Nevertheless, we are yet at a loss when we seek an explanation of the manifestations presented by certain subjects; but the science of to-day is not that of to-morrow; my science is not yours, and you will arrive at the comprehension of these phenomena in a future more or less distant.

INDEX.

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